Enantioselective Thiourea-Catalyzed Additions to Oxocarbenium Ions

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A. General Information.

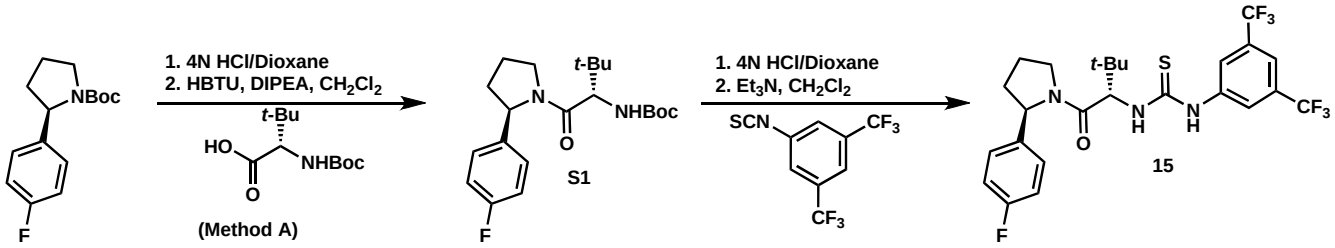
Catalyst screening reactions were performed in oven-dried 1-dram vials; all other reactions were performed in oven-dried round bottom flasks unless otherwise noted. The vials and flasks were fitted with rubber septa and reactions were conducted under a positive pressure of nitrogen. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. Commercial reagents were purchased from Sigma Aldrich, Alfa Aesar, Strem, or Lancaster, and used as received with the following exceptions: dichloromethane, tetrahydrofuran, diethyl ether, toluene, *t*-butyl methyl ether and methanol were dried by passing through columns of activated alumina; acetonitrile and dimethylformamide were dried by passing through columns of activated molecular sieves. Diisopropylamine, diisopropylethylamine, triethylamine and chlorotrimethylsilane were distilled from CaH_2 at 760 torr. *n*-Butyllithium and *s*-butyllithium were titrated following the procedure of Suffert.[1] Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian-Mercury-400 (400 MHz), Inova-500 (500 MHz), and Inova-600 (600 MHz) spectrometers. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$ = δ 7.27; C_6D_6 = 7.16). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$ = δ 77.0; C_6D_6 = δ 128.6). Data are represented as follows: chemical shift, multiplicity (br. s = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), integration. Infrared (IR) spectra were obtained using a Mattson Galaxy Series FTIR 3000 spectrophotometer referenced to a polystyrene standard. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 370 digital polarimeter. The mass spectral data were obtained at the Harvard University mass spectrometry facility. Chiral gas chromatography (GC) analysis was performed on a Hewlett-Packard 5890 gas chromatograph using an Alltech Cyclodex β (20 m x 0.25 mm) column, chiral HPLC analysis was performed using a Shimadzu VP-series instrument.

Silyl ketene acetals: Methyl trimethylsilyl dimethylketene acetal and 1-(*t*-butyldimethylsilyloxy)-1-methoxyethene were purchased from Aldrich and used as received. All other silyl ketene acetals were prepared from the commercially available methyl esters following the procedure reported by Wenzel and Jacobsen.[2]

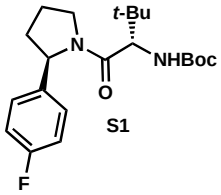
Abbreviations used: EtOAc – ethyl acetate, THF – tetrahydrofuran, MeOH – methanol, Et_2O – diethyl ether, AcOH – acetic acid, TBME – *t*-butylmethyl ether, DIPEA – diisopropyl ethylamine, NaOMe – sodium methoxide, HBTU – O-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate, EDC – 1-(3- (dimethyl-amino)propyl)-3-ethyl-carbodiimide hydrochloride, HOBt – 1-Hydroxybenzotriazole, Boc – *t*-butyl carbamate, ee – enantiomeric excess.

[1] Suffert, J. *J. Org. Chem.* **1989**, *54*, 509-510.
[2] Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964-12965.

B. General procedures for preparation of thiourea catalysts:



Step 1. Amide coupling: Method A. Preparation of *tert*-butyl (*S*)-1-((*R*)-2-(4-fluorophenyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (S1):

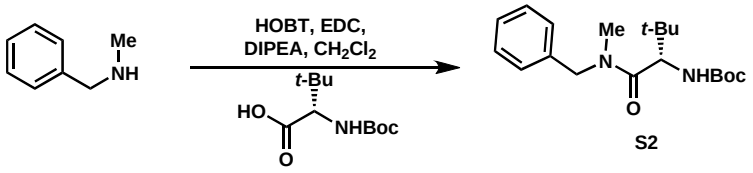


A flask was charged with (*R*)-*tert*-butyl 2-(4-fluorophenyl)pyrrolidine-1-carboxylate[3] (0.85 g, 3.21 mmol, 1.05 equiv) and HCl was added as a solution in dioxane (4.0 N, 20.9 mmol, 5.2 mL, 6.8 equiv). The reaction was stirred for 2 h at room temperature, then the flask was fitted with a vac-transfer tube and receiving flask. The receiving flask was cooled to –78 °C and the HCl/dioxane were removed in vacuo. The solid residue was placed under vacuum for 30 min, then flushed with N_2 and CH_2Cl_2 (6.0 mL) was added. A separate flask was charged with HBTU (1.15 g, 3.04 mmol, 1.0 equiv) and *N*-Boc-L-*tert*-leucine (0.70 g, 3.04 mmol, 1.0 equiv), and CH_2Cl_2 (8.0 mL) was added. To the resulting suspension was added DIPEA (1.68 mL, 9.63 mmol, 3.0 equiv), and after 10 min, the solution of the pyrrolidine salt (rinsed flask with 2 mL of CH_2Cl_2). After 30 min the reaction was homogenous, and stirring was continued for 12 h before dilution with Et_2O (20 mL). The cloudy mixture was washed once with 1N HCl (20 mL), once with saturated aqueous $NaHCO_3$ (20 mL), once with brine, and the organic layer was dried over anhydrous Na_2SO_4. Following concentration under reduced pressure, the residue was purified by silica gel chromatography (gradient elution, 1:1:18 to 1:1:3 EtOAc:CH_2Cl_2:Hexanes) to give amide **S1** (1.16 g, 92% yield) as a white foam. $[\alpha]_D^{27}$ = +32° (c = 0.42 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 3.2:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 7.23 (dd, *J*=8.4, 5.2 Hz, 2H§), 6.97-7.05 (m, 2H*), 6.88 (dd, *J*=8.8, 8.8 Hz, 2H*, 2H§), 5.35 (dd, *J*=8.4, 1.6 Hz, 1H§), 5.03-5.13 (m, 2H*, 1H§), 4.29 (d, *J*=10 Hz, 1H*), 4.15-4.20 (m, 1H*), 4.06 (d, *J*=10.8 Hz, 1H§), 3.67 (m, 1H*, 2H§), 2.16-2.32 (m, 1H*, 1H§), 1.75-2.00 (m, 3H*, 3H§), 1.43 (s, 9H*), 1.41 (s, 9H§), 1.00 (s, 9H*), 0.62 (s, 9H§). ^{13}C NMR (100 MHz, $CDCl_3$; compound exists as a 3.2:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 170.5*, 171.2§, 161.9§ (d, $J_{C\text{-}F}$=244.2 Hz), 161.4* (d, $J_{C\text{-}F}$=242.7Hz), 156.2*, 155.6§, 139.9§ (d, $J_{C\text{-}F}$=3.0 Hz), 138.4* (d $J_{C\text{-}F}$=3.0 Hz), 128.2§ (d, $J_{C\text{-}F}$=7.6 Hz), 126.6* (d, $J_{C\text{-}F}$=8.3 Hz), 115.3§ (d, $J_{C\text{-}F}$=21.2 Hz), 115.0* (d, $J_{C\text{-}F}$=21.2 Hz), 79.5*, 79.4§, 60.7§, 59.9*, 58.6*, 57.5§, 48.1*, 46.8§, 35.8§, 34.2*, 34.3§, 34.1*, 28.2*, 28.2§, 26.3*, 26.0§, 23.1*, 21.7§; FTIR (NaCl, thin film) 3445, 2971, 2873, 1713, 1652, 1509, 1426, 1367, 1232, 1170, 832, 732 cm^{-1}. LRMS (ES+) m/z: 379.5 $[M+H]^+$.

Note: Although the above procedure indicates that amide intermediate **S1** was purified by column chromatography, catalysts were routinely prepared with only a single chromatographic purification of the final thiourea.

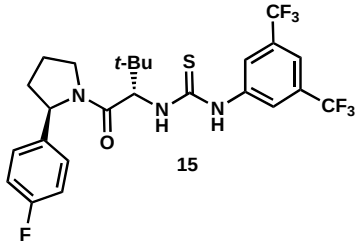
[3] Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. Y. *J. Am. Chem. Soc.* **2006**, *128*, 3538-3539.

Step 1. Amide Coupling, Method B. Preparation of *tert*-butyl (*S*)-1-(*N*-benzyl-*N*-methylcarbamoyl)-2,2-dimethylpropylcarbamate (S2).



To a solution of *N*-benzylmethylamine (2.13 mL, 16.5 mmol, 1.1 equiv) in CH_2Cl_2 (150 mL) in a 500 mL round-bottom flask was added DIPEA (3.92 mL, 22.5 mmol, 1.5 equiv), followed by HOBT (2.23 g, 16.5 mmol, 1.1 equiv), EDC (3.16 g, 16.5 mmol, 1.1 equiv), and *N*-Boc-L-*tert*-leucine (3.47g, 15.0 mmol, 1.0 equiv). The reaction was stirred at room temperature for 18 h, then diluted with 150 mL Et_2O and washed once each with 1N HCl (150 mL), saturate aqueous $NaHCO_3$ (150 mL) and brine (150 mL). The organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 4.89g (97% yield) of amide **S2** as a white foam. This material was used in the subsequent step without purification.

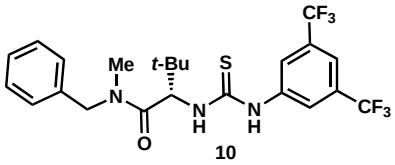
Step 2. Boc-deprotection and thiourea formation. Preparation 1-(3,5-bis(trifluoromethyl)phenyl)-3-((*S*)-1-((*R*)-2-(4-fluorophenyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)thiourea (15).



To a flask containing amide **S1** (1.16g, 3.0 mmol) was added HCl as a solution in dioxane (4.0 N, 19.7 mmol, 4.9 mL, 6.5 equiv). The reaction was stirred for 2 h at room temperature, after which time the flask was fitted with a vac-transfer tube and receiving flask. The receiving flask was cooled to –78 °C and the HCl/dioxane were removed in vacuo. The solid residue was placed under vacuum for 30 min, then flushed with N_2 and CH_2Cl_2 (15.0 mL) was added. To the resulting solution was added Et_3N (1.26 mL, 9.00 mmol, 3.0 equiv), followed by 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.61 mL, 3.30 mmol, 1.1 equiv). The reaction was stirred for 4 h at room temperature, and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (2:1 EtOAc:Hexanes) to give thiourea **15** (1.3 g, 79% yield) as a white solid. $[\alpha]_D^{26}$ = –2.84° (c = 1.0 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.2:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 9.53 (br. s, 1H§), 9.47 (br.s, 1H*), 8.00 (s, 2H§), 7.86 (s, 2H*), 7.66 (s, 1H§), 7.62 (s, 1H*), 7.52 (d, *J*=8.0 Hz, 1H*), 7.43 (d, *J*=10.0 Hz, 1H§), 7.31 (dd, *J*=9.0, J_{H-F}=5.5 Hz, 2H§), 7.06 (dd, *J*=9.0, J_{H-F}=9.0 Hz, 2H§), 6.89 (dd, *J*=8.5, J_{H-F}=5.5 Hz, 2H*), 6.66 (dd, *J*=8.5, J_{H-F}=8.5 Hz, 2H*), 5.81 (d, *J*=7.5 Hz, 1H§), 5.49 (d, *J*=9.5 Hz, 1H*), 5.30 (d, *J*=10.0 Hz, 1H§), 5.07 (d, *J*=7.5 Hz, 1H*), 4.42-4.48 (m, 1H*), 3.81 (dd, *J*=17.5, 9.0 Hz, 1H*), 3.54-3.57 (m, 2H§), 2.19-2.32 (m, 1H*, 1H§), 2.02-2.14 (m, 1H§), 1.76-2.05 (m, 3H*, 2H§), 1.15 (s, 9H*), 0.71 (s, 9H§); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a 2.2:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 181.4*, 181.1§, 172.5§, 170.5*, 162.3§ (d, J_{C-F}=244.8 Hz), 161.3* (d, J_{C-F}=243.1 Hz), 140.2§, 139.7*, 139.2§ (d, J_{C-F}=2.7 Hz), 137.1* (d, J_{C-F}=2.5 Hz), 132.1* (q, J_{C-F}=33.7 Hz), 131.9§ (q, J_{C-F}=33.6 Hz), 128.3§ (d, J_{C-F}=7.2 Hz), 126.7* (d, J_{C-F}=8.1Hz), 123.9* (m), 123.7§ (m), 123.1§ (q, J_{C-F}=271.2 Hz), 123.0* (q, J_{C-F}=271.2 Hz), 118.6* (m), 118.3§ (m), 115.6§ (d, J_{C-F}=21.0

Hz), 114.8* (d, $J_{C\text{-}F}$=21.9 Hz), 63.1*, 61.7[§], 61.6[§], 60.6*, 48.6*, 47.6[§], 35.9[§], 35.6*, 35.3[§], 34.2*, 26.9*, 26.8[§], 23.0*, 21.5[§]; FTIR (NaCl, thin film) cm^{-1}; LRMS (ES+) m/z: 550.6 $[M+H]^+$.

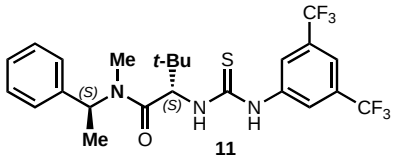
1-((*S*)-1-(*N*-benzyl-*N*-methylcarbamoyl)-2,2-dimethylpropyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (10).



10

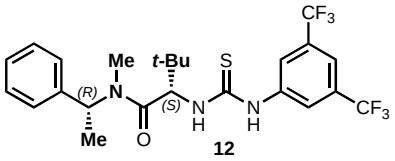
Prepared from 15.0 mmol of *N*-Boc-L-*tert*-leucine using amide coupling Method B, with a single silica gel chromatographic purification (gradient elution, 1:9 to 1:5 EtOAc:Hexanes) of the final thiourea to give 6.71 g (89% yield over three steps) of **10** as a white powder. $[\alpha]_D^{26}$ = –52.0 ° (c = 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 4.4:1 mixture of rotamers: the major rotamer is denoted by *) δ 9.29 (1 H, br. s.), 9.01 (1 H*, br. s.), 7.96 (2 H, s), 7.93 (1 H + 1H*, br. m), 7.85 (2 H*, s), 7.59 (1 H, s), 7.56 (1 H*, s), 7.29 (I H* + 1 H, s), 7.16-7.22 (4 H* + 4 H, m), 5.98 (1 H, d, *J*=9.5 Hz), 5.70 (1 H*, d, *J*=9.0 Hz), 5.15 (1 H, d, *J*=15.0 Hz), 4.97 (1 H*, d, *J*=14.5 Hz), 4.46 (1 H, d, *J*=15.0 Hz), 4.22 (1 H*, d, *J*=14.5 Hz), 3.26 (3 H*, s), 2.79 (3 H, s), 1.15 (9 H*, s), 1.14 (9 H, s); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a 4.4:1 mixture of rotamers, only the major rotamer is reported) δ 182.0, 174.1, 140.3, 135.7, 131.8 (q, $J_{C\text{-}F}$=33.8 Hz), 128.9, 128.3, 128.0, 124.4, 122.2, 118.5 (m), 61.4, 52.2, 36.8, 36.4, 27.5; FTIR (NaCl, thin film) 3324 (br), 3091 (m), 3067 (m), 3035 (m), 2969 (s), 1614 (s), 1532 (s), 1474 (m), 1384 (s), 1280 (s), 1179 (s), 1132 (s), 962 (m), 911 (m), 734 (m), 700 (m), 682 (m) cm^{-1}; HRMS (ES+) $[M+Na]^+$ calculated for $C_{23}H_{24}F_6NaN_3OS$: 505.1622, Found 528.1512.

1-((*S*)-1-(*N*-methyl-*N*-((*S*)-1-phenylethyl)carbamoyl)-2,2-dimethylpropyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (11). Prepared from 2.0 mmol of *N*-Boc-L-*tert*-leucine using amide coupling Method B, with a single silica gel chromatographic purification (gradient elution, 1:9 to 1:5 EtOAc:Hexanes) of the final thiourea to give 0.65 g (63% yield over three steps) of **11** as a white powder. $[\alpha]_D^{26}$ = –77.8° (c = 1.03 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 7.5:1 mixture of rotamers, the major rotamer is denoted by *) δ 9.27 (1 H, s), 8.97 (1 H*, s), 7.97 (2 H, s), 7.93 (2 H*, s), 7.76 (1 H*, d, *J*=9.1 Hz), 7.65 (1 H, s), 7.64 (1 H*, s), 7.23 - 7.44 (5 H + 5 H*, m), 6.12 (1 H, d, *J*=10.2 Hz), 5.97 (1 H*, q, *J*=7.0 Hz), 5.59 (1 H*, d, *J*=9.1 Hz), 2.94 (3 H*, s), 2.60 (3 H, s), 1.70 (3 H, d, *J*=6.6 Hz), 1.36 (3 H*, d, *J*=7.0 Hz), 1.19 (9 H, s), 1.12 (9 H*, s); ^{13}C NMR (CDCl3, 126 Mhz; compound exists as a 7.5:1 mixture of rotamers, the major rotamer is denoted by *) δ 181.8*, 181.2, 173.0*, 172.1, 140.2, 140.1*, 139.6*, 138.8, 132.2* (q, $J_{C\text{-}F}$=42.0 Hz), 128.9*, 128.8, 128.2, 128.0*, 127.7*, 127.5, 124.6* (q, $J_{C\text{-}F}$= 3.8 Hz), 121.9*, 118.9*, 61.9*, 60.7, 55.7, 52.3*, 36.7*, 31.2*, 28.4, 27.5*, 17.1, 15.1*; FTIR (NaCl, thin film) cm^{-1} 3321 (br), 3091 (w), 2066 (w), 3034 (w), 2971 (m), 1604 (s), 1532 (s), 1473 (s), 1383 (s), 1278 (s), 1178 (s), 1136 (s), 962 (m), 910 (m), 888 (m), 735 (m), 701 (m), 682 (m); HRMS (ES+) $[M+H]^+$ calculated for $C_{24}H_{28}F_6N_3OS$: 520.1852, Found: 520.1861.



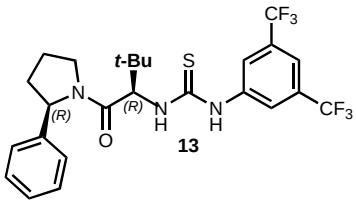
11

1-((*S*)-1-(*N*-methyl-*N*-((*R*)-1-phenylethyl)carbamoyl)-2,2-dimethylpropyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (12). Prepared from 2.0 mmol of *N*-Boc-L-*tert*-leucine using amide coupling Method B, with a single silica gel chromatographic purification (gradient elution, 1:9 to 1:5 EtOAc:Hexanes) of the final thiourea to give 0.65 g (51% yield over three steps) of **12** as a white powder. $[\alpha]_D^{26}$ = +79.0° (c = 1.05 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz; compound exists as



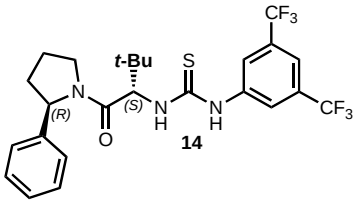
a 6:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 9.33 (br. s, 1 H§), 9.05 (br. s, 1 H*), 7.97 (d, *J*=9.2 Hz, 1 H*), 7.86 (s, 2 H§), 7.79 (s, 2 H*), 7.55 (s, 1 H*, 1H§), 7.36 - 7.42 (m, 2 H§), 7.30 - 7.35 (m, 2 H§), 7.00 - 7.11 (m, 5 H*), 5.93 (q, *J*=7.1 Hz, 1 H*, 1H§), 5.68 (d, *J*=9.4 Hz, 1 H*, 1H§), 3.05 (s, 3 H*), 2.68 (s, 3 H§), 1.71 (d, *J*=6.9 Hz, 3 H§), 1.53 (d, *J*=7.1 Hz, 3 H*), 1.19 (s, 9 H*), 1.13 (s, 9 H§); ^{13}C NMR ($CDCl_3$, 126 MHz; compound exists as a 6:1 mixture of rotamers, only the major rotamer is reported) δ 181.9, 173.2, 139.8, 138.7, 131.8 (q, $J_{C\text{-}F}$=33.0 Hz,), 128.4, 127.3, 126.6, 124.9, 122.9 (q, $J_{C\text{-}F}$=272.8 Hz), 118.7, 61.5, 60.0, 36.4, 31.3, 27.2, 16.7; FTIR (NaCl, thin film) 3317, 2972, 1607, 1534, 1384, 1279, 1178, 1137, 962, 699, 682 cm^{-1}; LRMS (ES+) m/z = 542.2 $[M+Na]^+$.

1-(3,5-bis(trifluoromethyl)phenyl)-3-((*R*)-3,3-dimethyl-1-oxo-1-((*R*)-2-phenylpyrrolidin-1-yl)butan-2-yl)thiourea (13).



Prepared from 2.85 mmol of *N*-Boc-D-*tert*-leucine using amide coupling Method A. Amide coupling product was purified by silica gel chromatography (1:4 EtOAc:Hexanes) to give 0.97 g (95% yield) as a white foam. Thiourea **13** was purified by silica gel chromatographic purification (gradient elution, 1:4 EtOAc:Hexanes) to give 1.25 g (82% yield over three steps) as a white foam. $[\alpha]_D$ = 130.1° (c = 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 399 MHz; compound exists as a 10:1 mixture of rotamers, chemical shifts of the major rotamer are reported) δ 9.01 (br. s, 1 H), 7.91 (s, 2 H), 7.79 (d, *J*=9.2 Hz, 1 H), 7.59 (s, 1 H), 7.24 (d, *J*=7.3 Hz, 2 H), 7.20 (d, *J*=7.0 Hz, 1 H), 7.12 (d, *J*=7.0 Hz, 2 H), 5.37 (d, *J*=8.8 Hz, 1 H), 4.94 (dd, *J*=7.0 Hz, 1 H), 4.39 - 4.48 (m, 1 H), 3.82 (ddd, *J*=10.3, 7.0 Hz, 1 H), 2.19 - 2.30 (m, 1 H), 2.05 - 2.15 (m, 1 H), 1.83 - 2.04 (m, 2 H), 0.99 (s, 9 H); ^{13}C NMR ($CDCl_3$, 126 MHz; compound exists as a 10:1 mixture of rotamers, the chemical shifts of the major rotamer are reported) δ 181.8, 172.2, 142.3, 140.2, 131.6 (q, $J_{C\text{-}F}$=33.9 Hz), 128.3, 127.0, 126.1, 123.5-124.0 (m), 123.0 (q, $J_{C\text{-}F}$=272.8 Hz), 117.9 - 118.6 (m), 63.5, 62.6, 49.8, 35.8, 34.0, 27.2, 24.8; FTIR (NaCl, thin film) 3318, 2970, 1611, 1539, 1473, 1440, 1385, 1278, 1178, 1134, 963, 699, 681 cm^{-1}; LRMS (ES+) m/z = 554.1 $[M+23]^+$.

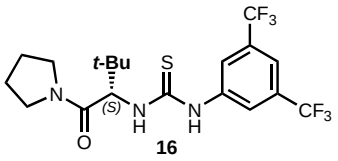
1-(3,5-bis(trifluoromethyl)phenyl)-3-((*S*)-3,3-dimethyl-1-oxo-1-((*R*)-2-phenylpyrrolidin-1-yl)butan-2-yl)thiourea (14).



Prepared from 1.46 mmol of *N*-Boc-L-*tert*-leucine using amide coupling Method A, with a single silica gel chromatographic purification (gradient elution, 1:9 to 1:3 EtOAc:Hexanes) of the final thiourea to give 0.32 g (42% yield over three steps) of **14** as a white powder. $[\alpha]^{26}_D$ = –3.30° (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.8:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 9.40 (br. s, 1 H§), 9.23 (br. s, 1 H*), 7.98 (s, 2 H§), 7.85 (s, 2 H*), 7.66 (s, 1 H§), 7.62 (s, 1 H*), 7.49 (d, *J*=8.7 Hz, 1 H*), 7.24-7.37 (m, 6 H§), 6.97-6.99 (m, 3 H*), 6.88 (dd, *J*=7.5, 2.5 Hz, 2 H*), 5.78 (d, *J*=7.8 Hz, 1 H§), 5.57 (d, *J*=9.6 Hz, 1 H*), 5.32 (d, *J*=8.2 Hz, 1 H§), 5.09 (d, *J*=7.8 Hz, 1 H*), 4.34 - 4.50 (m, 1 H*), 3.82 (dd, *J*=18.3, 10.1 Hz, 1 H*), 3.52 - 3.65 (m, 2 H§), 2.28 - 2.39 (m, 1 H§), 2.16 - 2.28 (m, 1 H*), 2.06 - 2.16 (m, 1 H§), 1.75 - 1.99 (m, 3 H* + 2 H§), 1.15 (s, 9 H*), 0.66 (s, 9 H§); ^{13}C NMR (126 MHz, $CDCl_3$; compound exists as a 1.8:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer denoted by §) δ 181.9*, 181.4§, 172.7§, 170.9*, 143.5§, 141.4*, 140.6§, 140.2*, 132.1* (q, $J_{C\text{-}}$

$_F$=33.9 Hz), 132.0[§] (q, J_{C-F}=33.8 Hz), 129.0[§], 128.3*, 128.0[§], 126.9*, 126.8[§], 125.2*, 124.4*, 124.1[§], 122.3[§], 122.2*, 118.7* (m), 118.5[§] (m), 63.1*, 62.6[§], 61.8[§], 61.3*, 49.0*, 47.9[§], 36.2[§], 36.0*, 35.5[§], 34.3*, 27.2*, 27.0[§], 23.2*, 21.8[§]; FTIR (NaCl, thin film) cm^{-1} 3325 (br), 2966 (m), 2875 (m), 1614 (s), 1528 (s), 1474 (m), 1449 (m), 1385 (S), 1278 (s), 1177 (s), 1134 (s), 962 (m), 910 (m) 886 (m), 734 (m), 700 (m), 682 (m); HRMS (ES+) $[M+H]^+$ calculated for $C_{25}H_{28}F_6N_3OS$: 532.1857, Found: 532.1871.

1-(3,5-bis(trifluoromethyl)phenyl)-3-((*R*)-3,3-dimethyl-1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)thiourea (16). Prepared from 1.0 mmol of *N*-Boc-L-*tert*-leucine using amide coupling Method B, with a single silica gel chromatographic purification (gradient elution, 1:9 to 1:3 EtOAc:Hexanes) of the final thiourea to give 0.28 g (61% yield over three steps) of **14** as a white powder. $[\alpha]^{26}_D$ = –19.2° (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.52 (br. s, 1 H), 7.96 (s, 2 H), 7.92 (d, *J*=9.3 Hz, 1 H), 7.60 (s, 1 H), 5.56 (d, *J*=9.3 Hz, 1 H), 4.16 (ddd, *J*=10.7, 7.3, 4.4 Hz, 1 H), 3.62 (ddd, *J*=10.1, 7.6 Hz, 1 H), 3.44 (ddd, *J*=12.0, 7.1, 5.4 Hz, 1 H), 3.26 (ddd, *J*=12.2, 7.8 Hz, 1 H), 1.87 - 2.04 (m, 2 H), 1.78 - 1.86 (m, 2 H), 1.15 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.3, 171.8, 140.5, 131.4 (q, J_{C-F}=33.7 Hz), 124.56 - 125.0 (m), 123.1 (d, *J*=272.3 Hz), 118.0 - 118.4 (m), 62.8, 48.5, 46.7, 36.0, 27.1, 25.8, 24.0; FTIR (NaCl, thin film) 3317, 2969, 2882, 1609, 1534, 1453, 1384, 1278, 1177, 1133, 936, 731 cm^{-1}; LRMS (ES+) m/z = 478.1 $[M+Na]^+$.



C. General procedure for thiourea-catalyzed addition of silyl ketene acetals to 1-chloroisochromans.

Method A (catalyst screening).

An oven-dried flask was charged with thiourea catalyst (0.015 mmol, 0.1 equiv), flushed with N_2, and TBME (1.3 mL) was added. The flask was cooled to –78 °C and the 1-chloroisochroman was added (0.20 mL of a 0.75 M stock solution in TBME, 0.15 mmol, 1.0 equiv), followed by the silyl ketene acetal (0.22 mmol, 1.5 equiv). The reaction was maintained at –78 °C for a given amount of time, then quenched at that temperature by addition of NaOMe (0.1 mL of 0.5 M solution in MeOH). The reaction was diluted with 1 mL of 50% Et_2O-Hexanes soution, filtered through a pipette containing ¾ inch of silica gel (to hydrolyze remaining silyl ketene acetal), and rinsed with 5 mL of the 50% Et_2O-Hexanes solution. The solvent was removed by rotary evaporation under reduced pressure to give the crude residue, which was purified by silica gel chromatography.

To facilitate determination of conversion by ^{1}H NMR analysis of the crude reaction mixtures, the 1-chloroisochroman stock solution contained 0.25 equiv of isochroman as an internal standard. Upon reaction quenching, any remaining 1-choroisochroman is converted quantitatively to the 1-methoxyisochroman. Thus, integration of the C1-proton of the 1-methoxyisochroman versus the C1 protons of isochroman correlates to unreacted starting material.

Method B.

In an oven-dried flask, 1-methoxyisochroman (**6**, 0.30 mmol, 1.0 equiv) was dried by azeotrope with benzene (2 x 2 mL), flushed with N_2, and dry CH_2Cl_2 (0.4 mL) was added. The solution was cooled to 0 °C and BCl_3 (1.0 M solution in hexanes, 0.10 mL, 0.35 equiv) was added dropwise. The reaction was warmed to room temperature and stirred for 1.5 h, after which time the solvent was removed in vacuo. The crude residue was placed under vacuum (1 torr) for 30 min, then flushed

with N_2 and dissolved in dry TBME (2.0 mL). The resulting solution was cooled to –78 °C and the thiourea catalyst was added as a solution in TBME (0.03 mmol, 1.0 mL of 0.03 M stock solution, 0.10 equiv), followed by the silyl ketene acetal (0.45 mmol, 1.5 equiv). After the given amount of time, the reaction was quenched by addition of NaOMe (0.2 mL of 0.5 M solution in MeOH). The reaction was diluted with 2 mL of 50% Et_2O-Hexanes solution, filtered through a 10 mL fritted funnel containing silica gel (to hydrolyze remaining silyl ketene acetal), and rinsed with 15 mL of the 50% Et_2O-Hexanes solution. The solvent was removed by rotary evaporation under reduced pressure to give the crude residue, which was purified by silica gel chromatography.

Isopropyl 2-(3,4-dihydro-1*H*-isochromen-1-yl)acetate (9a). Catalyst screen using catalysts **10-16** (see Table 1). All reactions were run for 6 h at –78 °C. Purified by silica gel chromatography (pipette column, 1:9 Et_2O:Hexanes). The enantiomeric excess was determined by chiral HPLC analysis (*S*, *S*-Whelk-01, 1 mL/min, 2% IPA in Hexanes, λ = 210 nm): t_R(major) = 12.0 min t_R(minor) = 10.8 min. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.15 - 7.21 (m, 2 H), 7.09 - 7.15 (m, 1 H), 7.05 (dd, *J*=5.5, 3.7 Hz, 1 H), 5.24 (dd, *J*=9.2, 3.7 Hz, 1 H), 5.10 (dt, *J*=12.7, 6.2 Hz, 1 H), 4.13 (ddd, *J*=11.4, 4.8 Hz, 1 H), 3.82 (ddd, *J*=11.8, 8.6, 3.9 Hz, 1 H), 2.97 (ddd, *J*=15.7, 9.5, 5.5 Hz, 1 H), 2.82 - 2.89 (dd, *J*=15.0, 3.5 Hz, 1 H), 2.71 - 2.77 (dd, *J*=15.0, 9.5 Hz, 1 H), 2.73 (dd, *J*=16.0, 8.2 Hz, 1 H), 1.26 (d, *J*=6.5 Hz, 3H), 1.25 (d, *J*=6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 170.7, 136.9, 133.9, 129.0, 126.6, 126.2, 124.5, 72.9, 67.9, 63.0, 42.0, 28.8, 21.8, 21.7; FTIR (NaCl, thin film) 2979, 2932, 2855, 1732, 1454, 1374, 1282, 1167, 1105, 749 cm^{-1}; LRMS (ES+) m/z = 257.1 $[M+Na]^+$.

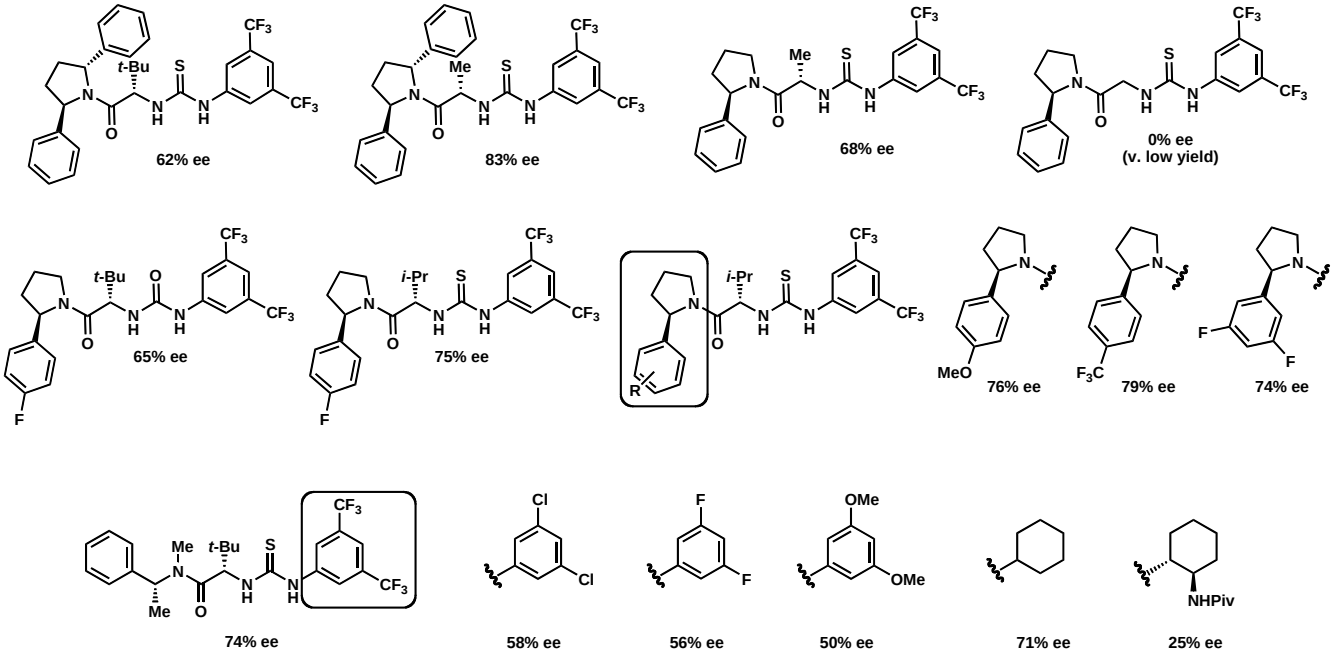
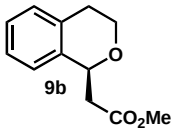
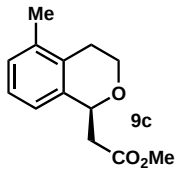


Figure S1. Enantioselectivities of additional catalysts screened using Method A (0.050 mmol scale) and silyl ketene acetal 9a, –78 °C.

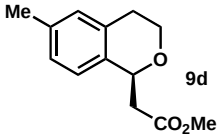
Methyl 2-((*S*)-3,4-dihydro-1*H*-isochromen-1-yl)acetate (9b). Method B: The reaction was run on 0.33 mmol scale for 6 h. The crude material was purified by silica gel chromatography (1:9 Et_2O:Hexanes) to give 59 mg (87% yield) of **9b** as a colorless oil. The enantiomeric excess was determined to be 85% by chiral HPLC analysis (*S*, *S*-Whelk-01, 1 mL/min, 2% IPA in Hexanes, λ = 210 nm): t_R(major) = 15.1 min t_R(minor) = 13.9 min. $[\alpha]_D^{26}$ = –93.9° (c = 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$, l00 MHz) δ 7.19 (ddd, *J*=8.9, 3.4, 3.4 Hz, 2H) 7.13 (dd, *J*=5.7, 4.1 Hz, 1 H), 7.05 (dd, *J*=5.3, 3.7 Hz, 1 H), 5.26 (dd, *J*=9.6, 3.2 Hz, 1 H), 4.14 (ddd, *J*=11.4, 4.7 Hz, 1 H), 3.83 (ddd, *J*=11.3, 9.0, 3.9 Hz, 1 H), 3.76 (s, 3 H), 2.99 (ddd, *J*=15.6, 8.9, 5.3 Hz, 1 H), 2.91 (dd, *J*=15.1, 3.4 Hz, 1 H), 2.78 (dd, *J*=15.3, 9.8 Hz, 1 H), 2.73 (ddd, *J*=16.3, 3.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.7, 136.6, 133.9, 129.0, 126.7, 126.2, 124.4, 72.9, 63.1, 51.8, 41.5, 28.8; FTIR (NaCl, thin film) 2952, 2925, 2857, 1743, 1506, 1435, 1284, 1167, 1111 cm^{-1}; LRMS (ES+) m/z = 229.1 $[M+Na]^+$.



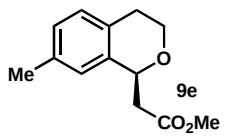
Methyl 2-((*S*)-3,4-dihydro-5-methyl-1*H*-isochromen-1-yl)acetate (9c). Method B: The reaction was run on 0.3 mmol scale for 7.5 h. The crude material was purified by silica gel chromatography (1:9 Et_2O:Hexanes) to give 47 mg (71% yield) of **9c** as a colorless oil. The enantiomeric excess was determined to be 90% by chiral HPLC analysis (*S*,*S*-Whelk-01, 1 mL/min, 2% IPA in Hexanes, λ = 210 nm): t_R(major) = 15.9 min, t_R(minor) = 14.9 min. $[\alpha]_D^{27}$ = –91.2° (c = 0.605, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.11 (dd, *J*=7.5, 7.5 Hz, 1 H), 7.06 (d, *J*=7.0 Hz, 1 H), 6.91 (d, *J*=7.5 Hz, 1 H), 5.25 (dd, *J*=10.0, 3.0 Hz, 1 H), 4.16 (ddd, *J*=11.5, 5.5, 4.0 Hz, 1 H), 3.84 (ddd, *J*=11.5, 9.0, 4.5 Hz, 1 H), 3.76 (s, 3 H), 2.89 (dd, *J*=15.0, 3.5 Hz, 1 H), 2.77 (dd, *J*=15.0, 9.5 Hz, 1 H), 2.74-2.83 (m, 1 H), 2.62 (ddd, *J*=16.5, 4.5, 4.5 Hz, 1 H), 2.24 (s, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.8, 136.4, 135.8, 130.8, 128.9, 127.6, 125.0, 72.9, 63.2, 51.8, 41.6, 28.4, 21.1; FTIR (NaCl, thin film) 2952, 2924, 2857, 1743, 1469, 1436, 1367, 1276, 1158, 1116, 1030, 785, 758 cm^{-1} LRMS (ES+) m/z = 243.1 $[M+Na]^+$.



Methyl 2-((*S*)-3,4-dihydro-6-methyl-1*H*-isochromen-1-yl)acetate (9d). Method B: The reaction was run on 0.30 mmol scale for 7.5 h. The crude material was purified by silica gel chromatography (1:9 Et_2O:Hexanes) to give 53 mg (82% yield) of **9d** as a colorless oil. The enantiomeric excess was determined to be 84% by chiral HPLC analysis (CHIRALPAK AS-H, 1 mL/min, 2% EtOH in Hexanes, λ = 210 nm): t_R(major) = 8.5 min, t_R(minor) = 7.1 min. $[\alpha]_D^{27}$ = –97.1° (c = 0.735, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.00 (d, *J*=8.5 Hz, 1 H), 6.94 (s, 1 H), 6.94 (d, *J*=8.0 Hz, 1 H), 5.22 (dd, *J*=10.0, 2.5 Hz, 1 H), 4.12 (ddd, *J*=11.5, 4.5, 4.5 Hz, 1 H), 3.80 (ddd, *J*=11.5, 9.5, 3.5 Hz, 1 H), 3.75 (s, 3 H), 2.95 (ddd, *J*=15.5, 9.5, 5.5 Hz, 1 H), 2.88 (dd, *J*=15.5, 3.5 Hz, 1 H), 2.74 (dd, *J*=15.0, 10.0 Hz, 1 H), 2.68 (ddd, *J*=16.0, 4.0, 4.0 Hz, 1 H), 2.31 (s, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.8, 136.3, 133.7, 133.6, 129.6, 127.1, 124.3, 72.9, 63.2, 51.8, 41.6, 28.8, 20.9; FTIR (NaCl, thin film) 2950, 2926, 2855, 1742, 1435, 1372, 1284, 1182, 1108, 1051, 822 cm^{-1}; LRMS (ES+) m/z = 243.1 $[M+Na]^+$.



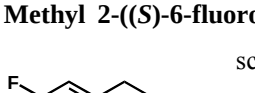
Methyl 2-((*S*)-3,4-dihydro-7-methyl-1*H*-isochromen-1-yl)acetate (9e). Method B: The reaction was run on 0.30 mmol scale for 7.5 h. The crude material was purified by silica gel chromatography (1:9 Et_2O:Hexanes) to give 54 mg (82% yield) of **9e** as a colorless oil. The enantiomeric excess was determined to be 87% by chiral HPLC analysis (*S*,*S*-Whelk-01, 1 mL/min, 2% IPA in Hexanes, λ = 210 nm): t_R(major) = 13.3 min, t_R(minor) = 12.6 min. $[\alpha]_D^{27}$ = 91.9° (c = 0.77, $CHCl_3$); ^{1}H



9e

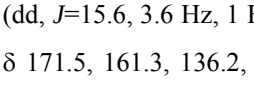
NMR ($CDCl_3$, 500 MHz) δ 7.02 (d, *J*=7.5 Hz, 1 H), 7.00 (d, *J*=8.0 Hz, 1 H), 6.85 (s, 1 H), 5.22 (dd, *J*= 9.5, 2.5 Hz, 1H), 4.11 (ddd, *J*=11.5, 5.0, 5.0 Hz, 1 H), 3.79 (ddd, *J*=11.5, 9.0, 3.5 Hz, 1 H), 3.76 (s, 3 H), 2.93 (ddd, *J*=16.0, 12.5, 6.0 Hz, 1 H), 2.89 (dd, *J*=15.0, 3.5 Hz, 1 H), 2.76 (dd, *J*=15.0, 10.0 Hz, 1 H), 2.68 (ddd, *J*=17.0, 4.0, 4.0 Hz, 1 H), 2.31 (s, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.7, 136.4, 135.7, 130.8, 128.9, 127.5, 124.9, 72.9, 63.1, 51.8, 41.6, 28.4, 21.1; FTIR (NaCl, thin film): 3022, 2952, 2854, 1742, 1436, 1283, 1197, 1164, 1109, 750 cm^{-1}; LRMS (ES+) m/z = 243.1 $[M+Na]^+$.

Methyl 2-((*S*)-6-fluoro-3,4-dihydro-1*H*-isochromen-1-yl)acetate (9f). Method B: The reaction was run on 0.30 mmol scale for 21 h. The crude material was purified by silica gel chromatography (1:4 Et_2O:Hexanes) to give 47 mg (70% yield) of **9f** as a colorless oil. The enantiomeric excess was determined to be 90% by chiral HPLC analysis (*S*,*S*-Whelk-01, 1 mL/min, 2% IPA in Hexanes, λ = 210 nm): t_R(major) = 16.4 min, t_R(minor) = 15.1 min. $[\alpha]_D^{27}$ = –107.1° (c = 0.83, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.00 (dd, *J*=8.4, 6.0 Hz, 1 H), 6.87 (ddd, *J*=8.4, 8.4, 2.4 Hz, 1 H), 6.82 (dd, *J*=9.0, 3.0 Hz, 1 H), 5.19 (dd, *J*=8.4, 2.4 Hz, 1 H), 4.14 (ddd, *J*=10.8, 4.8, 4.8 Hz, 1 H), 3.78 (ddd, *J*=11.4, 9.0, 3.6 Hz, 1 H), 3.74 (s, 3 H), 2.96 (ddd, *J*=15.6, 9.0, 6.0 Hz, 1 H), 2.85 (dd, *J*=15.6, 3.6 Hz, 1 H), 2.74 (dd, *J*=15.6, 8.0 Hz, 1 H), 2.69 (ddd, *J*=16.2, 4.2, 4.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.5, 161.3, 136.2, 132.3, 126.1, 115.3, 113.4, 72.6, 62.8, 51.9, 41.5, 28.9; FTIR (NaCl, thin film) 2954, 2857, 1742, 1500, 1437, 1285, 1236, 1164, 1106 cm^{-1}; LRMS (ES+) m/z = 247.1 $[M+23]^+$.

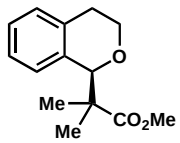


9f

Methyl 2-((*S*)-3,4-dihydro-6-methoxy-1*H*-isochromen-1-yl)acetate (9g). Method B: The reaction was run on 0.30 mmol scale for 22 h. The crude material was purified by silica gel chromatography (1:5 EtOAc:Hexanes) to give 68 mg (96% yield) of **9g** as a colorless oil. The enantiomeric excess was determined to be 74% by chiral HPLC analysis (CHIRALPAK AD-H, 1 mL/min, 5% IPA in Hexanes, λ = 210 nm): t_R(major) = 11.1 min, t_R(minor) = 10.6 min. $[\alpha]_D^{27}$ = –77.2° (c = 0.67, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.96 (d, *J*=8.5 Hz, 1 H), 6.75 (dd, *J*=8.6, 2.6 Hz, 1 H), 6.66 (d, *J*=2.3 Hz, 1 H), 5.20 (dd, *J*=9.6, 3.2 Hz, 1 H), 4.11 (ddd, *J*=11.3, 4.8 Hz, 1 H), 3.76 - 3.84 (m, 4 H), 3.75 (s, 3 H), 2.96 (ddd, *J*=15.6, 9.2, 5.3 Hz, 1 H), 2.86 (dd, *J*=15.1, 3.4 Hz, 1 H), 2.74 (dd, *J*=15.1, 9.6 Hz, 1 H), 2.69 (ddd, *J*=16.3, 4.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.7, 158.1, 135.2, 128.8, 125.5, 113.5, 112.5, 72.7, 63.0, 55.2, 51.8, 41.6, 29.1; FTIR (NaCl, thin film) 2953, 2930, 2849, 1740, 1611, 1504, 1435, 1285, 1243, 1164, 1108, 1036 cm^{-1}, LRMS (ES+) m/z = 259.1 $[M+Na]^+$.



Methyl 2-(3,4-dihydro-1*H*-isochromen-1-yl)-2-methylpropanoate (18a). Method B: The reaction was run on 0.30 mmol scale for 24 h. The crude material was purified by silica gel chromatography (1:9 Et_2O:Hexanes) to give 65 mg (92% yield) of **18a** as a colorless oil. The enantiomeric excess was determined to be 92% by chiral GC analysis (β-cyclodex, 105° C isothermal, 7 psi): t_R(major)= 190.5 min, t_R(minor)=192.8 min. $[\alpha]_D^{26}$ = –113.6° (c = 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.16 (m, 2H), 7.11 (d, *J*=8.5 Hz, 1H), 6.97 (d, *J*=7.5 Hz, 1H), 5.17 (s, 1H), 4.14 (ddd, *J*=10.5, 5.0, 2.0 Hz, 1H), 3.76 (s, 3H), 3.78 (ddd, *J*=11.5, 10.5, 2.5

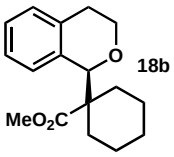


18a

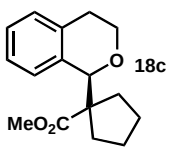
Hz, 1H), 2.99 (ddd, *J*=16.0, 11.5, 5.0 Hz, 1H), 2.53 (d, *J*=15.5 Hz, 1H), 1.13 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.6, 135.4, 134.8, 128.7, 126.4, 125.8, 125.7, 80.1, 64.0, 51.9, 49.0, 30.1, 21.1, 20.9; IR (NaCl, thin film) 2980, 2948, 2858, 1738, 1467, 1267, 1190, 1132, 1105, 748 cm^{-1}. LRMS (ES+) m/z = 257.1 $[M+Na]^+$.

5.0 mmol scale: A flame-dried 100 mL flask was charged with 1-methoxyisochroman (**6**, 0.84 g, 5.00 mmol, 1.0 equiv), flushed with N_2, and dry CH_2Cl_2 (4.0 mL) was added. The solution was cooled to 0 °C and BCl_3 (1.0 M in hexanes, 2.00 mL, 2.00 mmol, 0.4 equiv) was added dropwise over 5 min. The reaction was stirred for 5 min at 0 °C then 1.5 h at room temperature, after which time the flask was quickly fitted with an oven-dried vac-transfer tube and receiving flask under N_2. The receiving flask was cooled to –78 °C, and the solvent was removed in vacuo (1 torr). Once the solvent was removed, the vac-transfer tube was disconnected and the flask was placed under vacuum for an additional 30 min, then back-filled with N_2. The flask was fitted with a septum and TBME (40 mL) was added. The solution was cooled to –78 °C and thiourea **15** (137 mg, 0.25 mmol, 0.05 equiv) was added as a solution in TBME (8 mL, plus 2 mL wash). After 5 min, silyl ketene acetal **17a** (1.23 mL, 6.25 mmol, 1.25 equiv) was added dropwise and the flask was packed in dry ice in an insulated container for 22 h, then quenched at –78 °C with NaOMe (0.5 M solution in MeOH, 3.3 mL). The heterogeneous mixture was warmed to room temperature, diluted with 30 mL 1:1 Et_2O:Hexanes, filtered through a 60 mL fritted funnel containing 1 cm silica gel, and rinsed with 40 mL (total) 1:1 Et_2O/Hexanes. The solvent was removed by rotary evaporation under reduced pressure and the crude residue was purified by silica gel chromatography (1:9 Et_2O:Hexanes) to give **18a** (1.11g, 95% yield) as a colorless oil. The enantiomeric excess was determined to be 91% by chiral GC analysis (see above for conditions).

Methyl 1-(3,4-dihydro-1*H*-isochromen-1-yl)cyclohexanecarboxylate (18b). Method B: The reaction was run on 0.3 mmol scale for 24 h. The crude material was purified by silica gel chromatography (1:9 Et_2O:Hexanes) to give 69 mg (84% yield) of **18b** as a white solid. The enantiomeric excess was determined to be 94% by chiral HPLC analysis (Chiralcel OD-H, 0.5 mL/min, 1% IPA in Hexanes, λ = 210 nm): t_R(major) = 14.7 min, t_R(minor) = 11.1 min. $[\alpha]_D^{26}$ = –184.9° (c = 0.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.14 - 7.19 (m, 2H), 7.10 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.97 (dd, *J* = 8.5, 1.5 Hz, 1H), 4.97 (s, 1H), 4.14 (ddd, *J* = 10.5, 5.0, 1.5 Hz, 1H), 3.72 (s, 3H), 3.52 (ddd, *J* = 11.0, 11.0, 2.5 Hz, 1H), 2.95 (ddd, *J* = 16.0, 11.5, 4.5 Hz, 1H), 2.51 (d, *J* = 15.5 Hz, 1H), 2.13 (d, *J* = 13.0 Hz, 1H), 1.90 (d, *J* = 12.5 Hz, 1H), 1.59 (m, 3H), 1.42 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1H), 1.23 - 1.36 (m, 3H), 1.02 - 1.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 175.8, 136.8, 134.1, 128.4, 126.6, 126.5, 125.5, 81.1, 63.8, 54.9, 51.5, 30.4, 29.6, 29.4, 25.7, 23.2, 23.1; FTIR (NaCl, thin film) 2935, 2855, 1736, 1453, 1215, 1131, 1103, 748 cm^{-1}; LRMS (ES+) m/z = 297.1 $[M+Na]^+$.

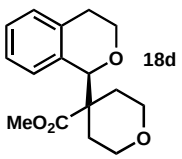


Methyl 1-((*R*)-3,4-dihydro-1*H*-isochromen-1-yl)cyclopentanecarboxylate (18c). Method B: The reaction was run on 0.31 mmol scale for 24 h. The crude material was purified by silica gel chromatography (1:9 Et_2O:Hexanes) to give 66 mg (85% yield) of **18c** as a colorless oil. The enantiomeric excess was determined to be 92% by chiral HPLC analysis (CHIRALPAK AD-H, 1.0 mL/min, 2% IPA in Hexanes, λ = 210 nm): t_R(major) = 5.2 min, t_R(minor) = 6.1 min. $[\alpha]_D^{26}$ = 111.8° (c = 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.09-7.17 (m, 3H), 6.96 (d, *J* = 7.0 Hz, 1H), 5.23 (s, 1H), 4.17 (ddd, *J* = 11.0, 5.5, 2.5 Hz, 1H), 3.72 (s, 3H), 3.67 (ddd, *J* = 11.0, 11.0, 3.0 Hz, 1H), 3.00 (ddd, *J* = 16.5, 11.0, 5.5 Hz, 1H), 2.59 (d, *J* = 16.0 Hz, 1H), 1.97-2.05 (m, 3H), 1.55-1.63 (m, 5H); ^{13}C

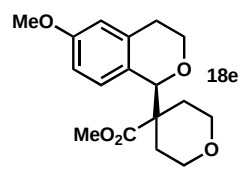


NMR ($CDCl_3$, 126 MHz) δ 171.7, 136.3, 136.0, 129.0, 126.6, 126.1, 125.5, 79.5, 64.4, 60.2, 52.2, 34.8, 31.9, 30.0, 26.0, 25.8; IR (NaCl, thin film) 2951, 2869, 1733, 1452, 1267, 1232, 1192, 1162, 1108, 743 cm^{-1}; LRMS (ES+) m/z = 283.1 $[M+Na]^+$.

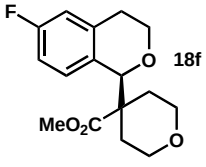
Methyl tetrahydro-4-((*R*)-3,4-dihydro-1*H*-isochromen-1-yl)-2*H*-pyran-4-carboxylate (18d). Method B: The reaction was run on 0.30 mmol scale for 24 h. The crude material was purified by silica gel chromatography (1:9 EtOAc:Hexanes) to give 89 mg (87% yield) of **18d** as a white solid. The enantiomeric excess was determined to be 93% by chiral HPLC analysis (Chiralcel OD-H, 1.0 mL/min, 5% IPA in Hexanes, λ = 210 nm): t_R(major) = 7.9 min, t_R(minor) = 7.3 min. $[\alpha]_D^{26}$ = –97.6° (c = 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.15-7.23 (m, 2 H), 7.12 (d, *J*=7.8 Hz, 1 H), 6.97 (d, *J*=6.8 Hz, 1 H), 5.00 (s, 1 H), 4.15 (ddd, *J*=10.6, 5.0, 2.0 Hz, 1 H), 3.83 (dd, *J*=12.0, 3.5 Hz, 2 H) 3.75 (s, 3 H), 3.53 (ddd, *J*=11.7, 2.0 Hz, 1 H), 3.38 – 3.45 (m, 2H), 2.93 (ddd, *J*=15.9, 11.5, 4.9 Hz, 1 H), 2.54 (d, *J*=15.6 Hz, 1 H), 2.02 (dd, *J*=13.4, 1.2 Hz, 1 H), 1.83 (dd, *J*=8.8, 3.9 Hz, 2 H), 1.74 (ddd, *J*=12.9, 4.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 174.9, 136.7, 133.2, 128.5, 126.7, 126.4, 125.7, 80.4, 65.3, 65.2, 63.7, 52.5, 51.8, 30.2, 29.7, 29.5; FTIR (thin film) 2956, 2857, 1730, 1446, 1301, 1220, 1198, 1135, 1101, 1034, 752 cm^{-1}; LRMS (ES+) m/z = 291.1 $[M+Na]^+$.



Methyl tetrahydro-4-((*R*)-3,4-dihydro-6-methoxy-1*H*-isochromen-1-yl)-2*H*-pyran-4-carboxylate (18e). Method B: The reaction was run on 0.30 mmol scale for 24 h. The crude material was purified by silica gel chromatography (1:4 EtOAc:Hexanes) to give 87 mg (95% yield) of **18e** as a white solid. The enantiomeric excess was determined to be 88% by chiral HPLC analysis (CHIRALPAK AS-H, 1.0 mL/min, 5% IPA in Hexanes, λ = 210 nm): t_R(major) = 12.1 min, t_R(minor) = 10.6 min. $[\alpha]_D^{26}$ = –132.1° (c = 0.88, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.88 (d, *J*=8.2 Hz, 1 H), 6.73 (dd, *J*=8.5, 2.5 Hz, 1 H), 6.65 (d, *J*=2.7 Hz, 1 H), 4.95 (s, 1 H), 4.12 (ddd, *J*=10.6, 4.9, 1.8 Hz, 1 H), 3.83 (dd, *J*=11.7, 3.0 Hz, 2 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 3.51 (ddd, *J*=11.0, 2.3 Hz, 1 H), 3.36-3.47 (m, 2 H), 2.90 (ddd, *J*=15.9, 11.6, 5.0 Hz, 1 H), 2.49 (d, *J*=15.6 Hz, 1 H), 2.00 (dd, *J*=13.3, 1.8 Hz, 1 H), 1.78-1.87 (m, 2 H), 1.73 (ddd, *J*=13.5, 13.5, 5.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 175.1, 158.2, 138.2, 127.6, 125.3, 113.5, 111.8, 80.2, 65.4, 65.3, 63.6, 55.2, 52.6, 51.8, 30.6, 29.7, 29.6; FTIR (NaCl, thin film) 2956, 2854, 1732, 1611, 1503, 1446, 1284, 1259, 1245, 1219, 1195, 1134, 1102, 1035 cm^{-1}; LRMS (ES+) m/z = 329.1 $[M+Na]^+$.

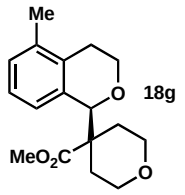


Methyl 4-((*R*)-6-fluoro-3,4-dihydro-1*H*-isochromen-1-yl)-tetrahydro-2*H*-pyran-4-carboxylate (18f). Method B: The reaction was run on 0.30 mmol scale for 21h. The crude material was purified by silica gel chromatography (1:5 EtOAc:Hexanes) to give 62 mg (70% yield) of **18f** as a white solid. The enantiomeric excess was determined to be 95% by chiral HPLC analysis (CHIRALPAK AD-H, 1.0 mL/min, 5% EtOH in Hexanes, λ = 210 nm): t_R(major) = 13.1 min, t_R(minor) = 15.7 min. $[\alpha]_D^{26}$ = –106.0° (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.92 (dd, *J*=8.5, J_{H-F}=5.5 Hz, 1 H), 6.87 (ddd, *J*=8.5, 2.0, $J_{H=F}$=8.5 Hz, 1 H), 6.83 (dd, *J*=2.5, J_{H-F}=9.0 Hz, 1 H), 4.95 (s, 1 H), 4.13 (ddd, *J*=10.5, 5.0, 1.5 Hz, 1 H), 3.83 (dd, *J*=11.5, 4.0 Hz, 2 H), 3.73 (s, 3 H), 3.50 (ddd, *J*=11.0, 11.0, 2.5 Hz, 1 H), 3.41 (m, 2 H), 2.90 (ddd, *J*=15.5, 11.5, 5.0 Hz, 1 H), 2.51 (d, *J*=15.5 Hz, 1 H), 1.99 (dd, *J*=13.5 Hz, 2.0 Hz, 1 H), 1.77 (m, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 174.8, 161.4 (d, J_{C-F}=246.2 Hz),



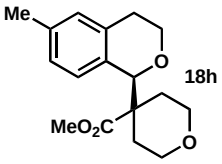
139.1 (d, $J_{C\text{-}F}$=7.3 Hz), 128.9 (d, $J_{C\text{-}F}$=2.76 Hz), 128.0 (d, $J_{C\text{-}F}$=Hz), 115.1 (d, $J_{C\text{-}F}$=21.1 Hz), 113.0 (d, $J_{C\text{-}F}$=22.0 Hz), 80.1, 65.3, 65.2, 63.4, 52.5, 51.9, 30.3, 29.9, 29.5; IR (NaCl, thin film): 2956, 2940, 2857, 1732, 1616, 1499, 1238, 1220, 1196, 1135, 1102 cm^{-1}; LRMS (ES+) m/z = 317.1 $[M+Na]^+$.

Methyl tetrahydro-4-((*R*)-3,4-dihydro-5-methyl-1*H*-isochromen-1-yl)-2*H*-pyran-4-carboxylate (18g). Method B: The



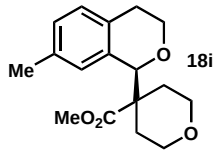
reaction was run on 0.30 mmol scale for 24 h. The crude material was purified by silica gel chromatography (1:9 EtOAc:Hexanes) to give 62 mg (70% yield) of **18g** as a viscous colorless oil. The enantiomeric excess was determined to be 97% by chiral HPLC analysis (Chiralcel OD-H, 1.0 mL/min, 5% IPA in Hexanes, λ = 210 nm): t_R(major) = 9.8 min, t_R(minor) = 7.9 min. $[\alpha]_D^{26}$ = –83.5° (c = 0.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.08 (s, 1 H), 7.09 (dd, *J*=9.4, 8.0 Hz, 1 H), 6.79-6.84 (m, 1 H), 5.01 (s, 1 H), 4.18 (ddd, *J*=10.8, 5.2, 1.9 Hz, 1 H), 3.79-3.86 (m, 2 H), 3.75 (s, 3 H), 3.55 (ddd, *J*=11.0, 2.6 Hz, 1 H), 3.38-3.47 (m, 2 H), 2.72 (ddd, *J*=16.2, 11.3, 5.0 Hz, 1 H), 2.56 (ddd, *J*=16.0, 1.8 Hz, 1 H), 2.26 (s, 3 H), 2.00 (ddd, *J*=13.5, 4.1, 2.1 Hz, 1 H), 1.71-1.85 (m, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 174.8, 135.3, 135.0, 132.9, 128.0, 125.0, 123.7, 80.1, 65.1, 65.0, 63.2, 52.4, 51.5, 29.7, 29.1, 26.8, 18.8; FTIR (NaCl, thin film) 2955, 2855, 1732, 1468, 1446, 1219, 1196, 1139, 1108, 1080, 1034 cm^{-1}; LRMS (ES+) m/z = 313.1 $[M+Na]^+$.

Methyl tetrahydro-4-((*R*)-3,4-dihydro-6-methyl-1*H*-isochromen-1-yl)-2*H*-pyran-4-carboxylate (18h). Method B: The



reaction was run on 0.30 mmol for 27 h. The crude material was purified by silica gel chromatography (1:9 EtOAc:Hexanes) to give 66 mg (76% yield) of **18h** as a white solid. The enantiomeric excess was determined to be 94% by chiral HPLC analysis (CHIRALPAK AS-H, 1.0 mL/min, 2% EtOH in Hexanes, λ = 210 nm): t_R(major) = 6.5 min, t_R(minor) = 6.1 min. $[\alpha]_D^{26}$ = –108.4° (c = 0.89, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.99 (d, *J*=8.2 Hz, 1 H), 6.94 (s, 1 H), 6.85 (d, *J*=7.8 Hz, 1 H), 4.97 (s, 1 H), 4.13 (ddd, *J*=10.5, 5.0, 1.8 Hz, 1 H), 3.83 (dd, *J*=11.4, 3.7 Hz, 2 H), 3.75 (s, 3 H), 3.52 (ddd, *J*=11.0, 11.0, 2.3 Hz, 1 H), 3.38-3.48 (m, 2 H), 2.89 (ddd, *J*=15.8, 11.4, 4.8 Hz, 1 H), 2.49 (d, *J*=15.6 Hz, 1 H), 2.32 (s, 3 H), 2.01 (d, *J*=12.8 Hz, 1 H), 1.79-1.85 (m, 2 H), 1.74 (ddd, *J*=13.2, 4.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 175.3, 136.8, 136.7, 130.5, 129.4, 126.9, 126.6, 80.6, 65.6, 65.5, 64.0, 52.8, 52.0, 30.5, 30.0, 29.8, 21.2; FTIR (NaCl, thin film) 2956, 2856, 1733, 1446, 1218, 1194, 1134, 1100, 1034, 842 cm^{-1}; LRMS (ES+) m/z = 292.2 $[M+H]^+$.

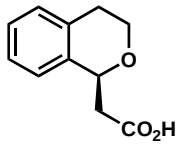
Methyl tetrahydro-4-((*R*)-3,4-dihydro-7-methyl-1*H*-isochromen-1-yl)-2*H*-pyran-4-carboxylate (18i). Method B: The



reaction was run on 0.30 mmol for 20h. The crude material was purified by silica gel chromatography (1:9 EtOAc:Hexanes) to give 61 mg (70% yield) of **18i** as a white solid. The enantiomeric excess was determined to be 92% by chiral HPLC analysis (CHIRALPAK AS-H, 1.0 mL/min, 2% EtOH in Hexanes, λ = 210 nm): t_R(major) = 6.3 min, t_R(minor) = 6.0 min. $[\alpha]_D^{26}$ = –120.6° (c = 0.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.00 (m, 2 H), 6.75 (s, 1 H), 4.94 (s, 1 H), 4.12 (ddd, *J*=10.5, 5.0, 2.0 Hz, 1 H), 3.81-3.85 (m, 2 H), 3.75 (s, 3 H), 3.49 (ddd, *J*= 12.0, 12.0, 2.0 Hz, 1 H) 3.37-3.48 (m, 2 H), 2.86 (ddd, *J*=16.5, 12.0, 5.0 Hz, 1 H), 2.48 (d, *J*=15.5 Hz, 1 H), 2.31 (s, 3 H), 2.01 (dd, *J*=13.5, 2.0 Hz, 1 H), 1.79-1.86 (m, 2 H), 1.72 (ddd, *J*=13.0, 13.0, 5.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 175.1, 135.2, 133.7, 133.0, 128.3, 127.6, 127.1, 80.4, 65.3, 65.3, 63.9, 52.7, 51.7, 29.9, 29.6,

29.4, 21.2; FTIR (NaCl, thin film): 2952, 2876, 2857, 1723, 1506, 1444, 1217, 1194, 1132, 1101 cm^{-1}; LRMS (ES+) m/z = 313.1 $[M+Na]^+$.

Assignment of absolute stereochemistry: saponification of isopropyl 2-(3,4-dihydro-1*H*-isochromen-1-yl)acetate (9a).



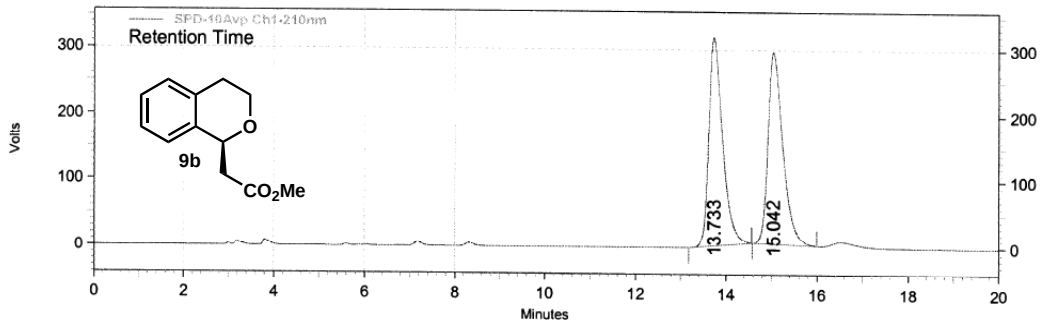
To a solution of **9a** (30 mg, 0.13 mmol, 1.0 equiv; 82% ee) in MeOH (0.75 mL) was added 0.5 M LiOH (1.0 mL, 1.0 mmol, 3.8 equiv). The reaction was stirred at room temperature for 15 h, then acidified by addition of 0.5 M citric acid (1.5 mL). The MeOH was removed under reduced pressure, and the aqueous residue was partitioned with CH_2Cl_2 (3 X 10 mL). The organics were washed once with brine (15 mL), and dried over Na_2SO_4. Filtration followed by rotary evaporation under reduced pressure provided a crude residue that was purified by sílica gel chromatography provide **9a** (21 mg, 85% yield) as a colorless oil. The ^1H NMR data were identical to that reported by TenBrink and coworkers.[4] $[\alpha]_D^{29} = -85°$ (c = 1.05, CH_2Cl_2). The observed rotation corresponds to product of 65% ee, indicating that some epimerization occured under the saponification conditions. TenBrink and coworkers report $[\alpha]_D = -132°$ (c = 0.98, CH_2Cl_2) for (*S*)-(−)-(isochroman-1-yl)acetic acid.

[4] TenBrink, R. E.; Bergh, C. L.; Duncan, J. N.; Harris, D. W.; Huff, R. M.; Lahti, R. A.; Lawson, C. F.; Lutzke, B. S.; Martin, I. J.; Rees, S. A.; Schlachter, S. K.; Sih, J. C.; Smith, M. W. *J. Med. Chem.* **1996**, *39*, 2435-2437.

D. Chromatograms of racemic and enantiomerically enriched isochromans.

Methyl 2-((*S*)-3,4-dihydro-1*H*-isochromen-1-yl)acetate (9b).

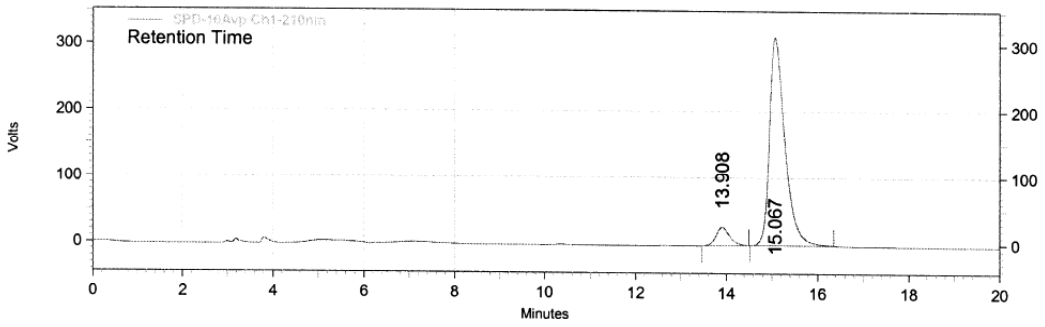
Racemic **9b** ((*S*,*S*)-Whelk-01 (Pirkle), 98:2 hexane:*i*-PrOH, 1 mL/min, λ=210 nm):



SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
13.733	6650757	50.21	315544	52.01
15.042	6593836	49.79	291160	47.99

Enantiomerically enriched **9b** (85% ee):

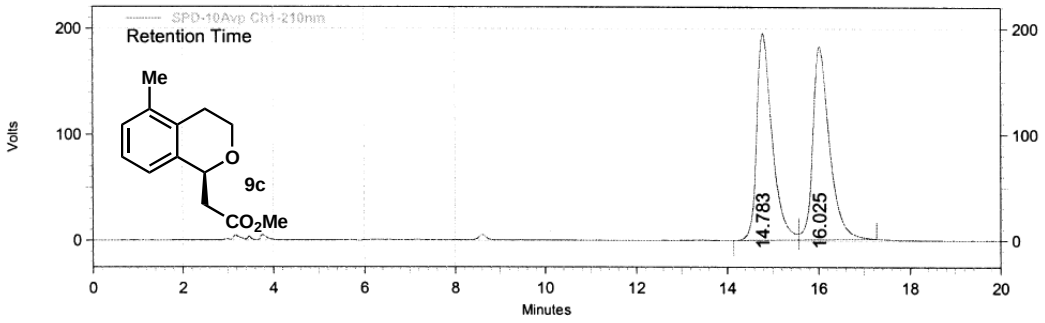


SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
13.908	573379	7.26	27446	8.03
15.067	7326044	92.74	314420	91.97

Methyl 2-((*S*)-3,4-dihydro-5-methyl-1*H*-isochromen-1-yl)acetate (9c).

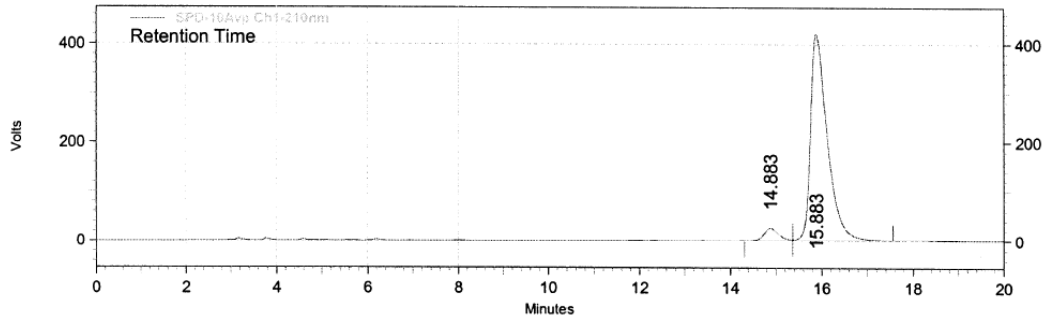
Racemic **9c** ((*S*,*S*)-Whelk-01 (Pirkle), 98:2 hexane:*i*-PrOH, 1 mL/min, λ=210 nm):



SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
14.783	4564364	49.67	195442	51.71
16.025	4625099	50.33	182482	48.29

Enantiomerically enriched **9c** (90% ee):

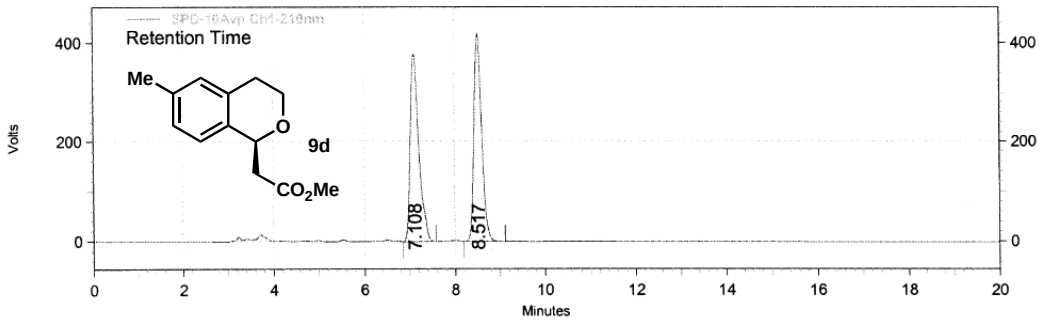


SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
14.883	585919	5.17	25733	5.78
15.883	10755064	94.83	419787	94.22

Methyl 2-((*S*)-3,4-dihydro-6-methyl-1*H*-isochromen-1-yl)acetate (9d)

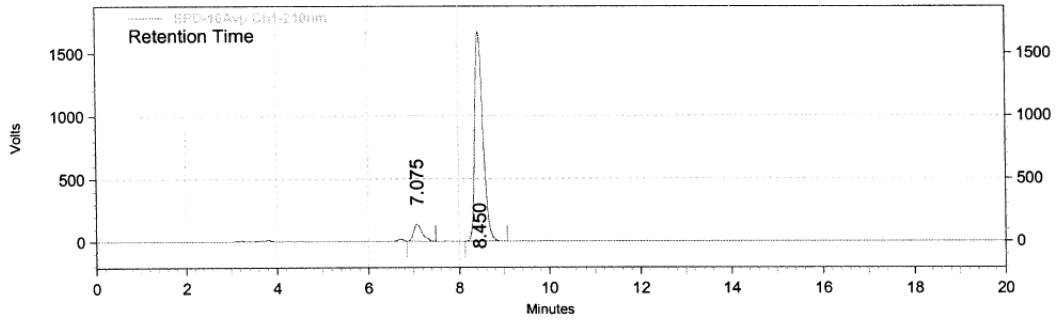
Racemic **9d** (CHIRALPAK AS-H, 98:2 hexane:EtOH, 1 mL/min, λ=210 nm):



SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
7.108	4957274	49.97	378302	47.42
8.517	4962858	50.03	419548	52.58

Enantiomerically enriched **9d** (84% ee):

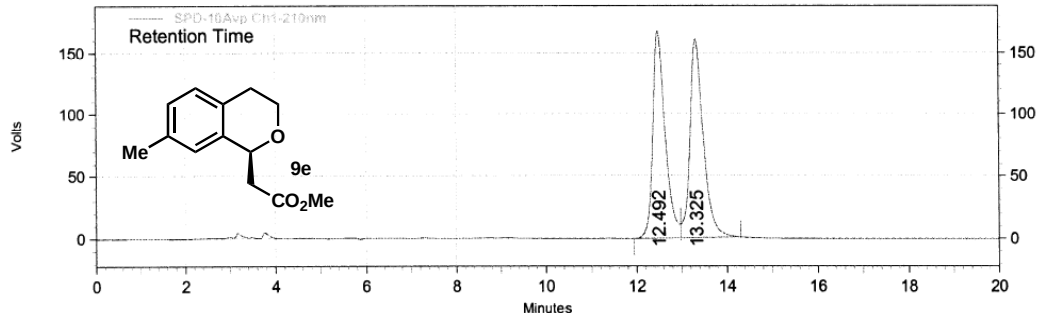


SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
7.075	1793657	7.87	137557	7.60
8.450	21009085	92.13	1672774	92.40

Methyl 2-((*S*)-3,4-dihydro-7-methyl-1*H*-isochromen-1-yl)acetate (9e).

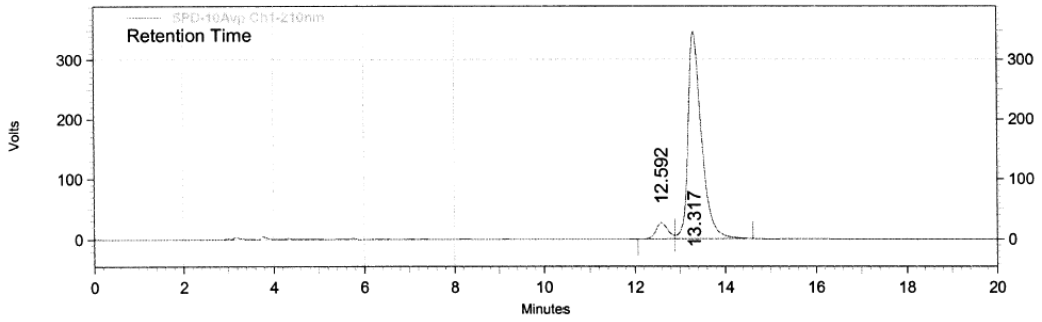
Racemic **9e** ((*S*,*S*)-Whelk-01 (Pirkle), 98:2 hexane:*i*-PrOH, 1 mL/min, λ=210 nm):



SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
12.492	3191152	49.23	166979	51.06
13.325	3291029	50.77	160063	48.94

Enantiomerically enriched **9e** (87% ee):

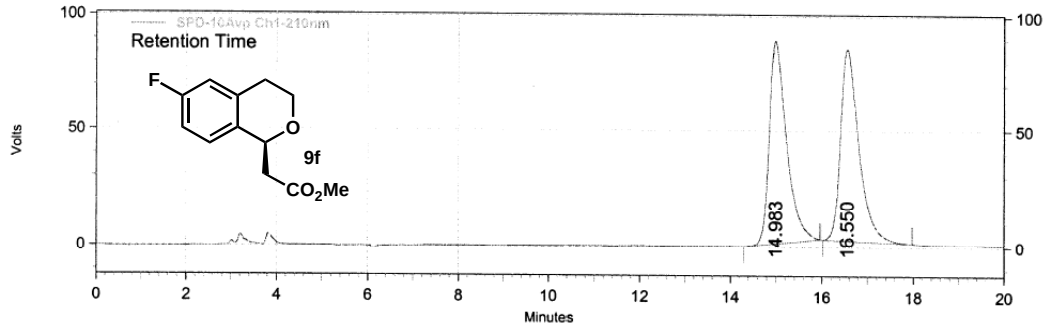


SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
12.592	492153	6.46	26903	7.18
13.317	7122164	93.54	347791	92.82

Methyl 2-((*S*)-6-fluoro-3,4-dihydro-1*H*-isochromen-1-yl)acetate (9f).

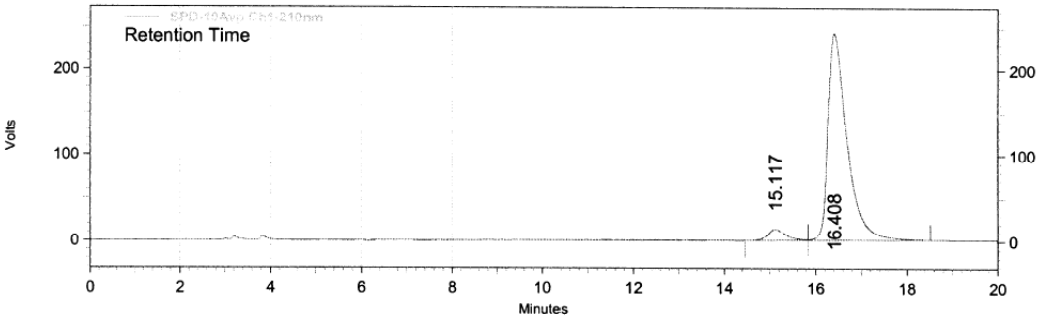
Racemic **9f** (*S,S*-Whelk-01 (Pirkle), 98:2 Hexanes:*i*-PrOH, 1 mL/min, λ = 210 nm):



SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
14.983	2291918	49.87	87880	51.34
16.550	2303696	50.13	83292	48.66

Enantiomerically enriched **9f** (90% ee):

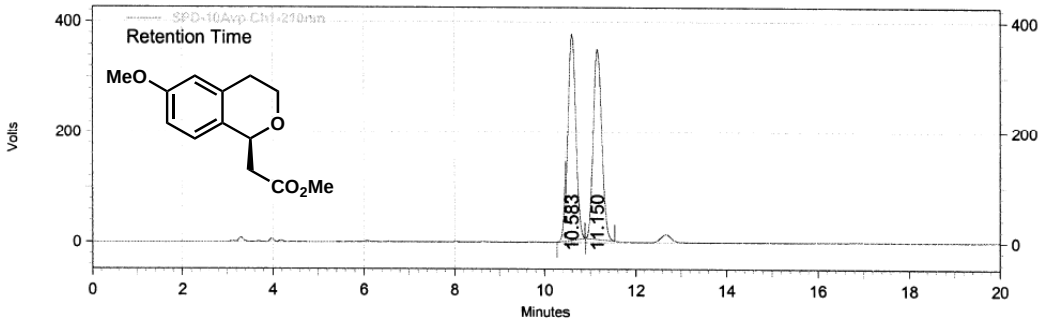


SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
15.117	357059	4.87	13083	5.12
16.408	6978343	95.13	242287	94.88

Methyl 2-((*S*)-3,4-dihydro-6-methoxy-1*H*-isochromen-1-yl)acetate (9g).

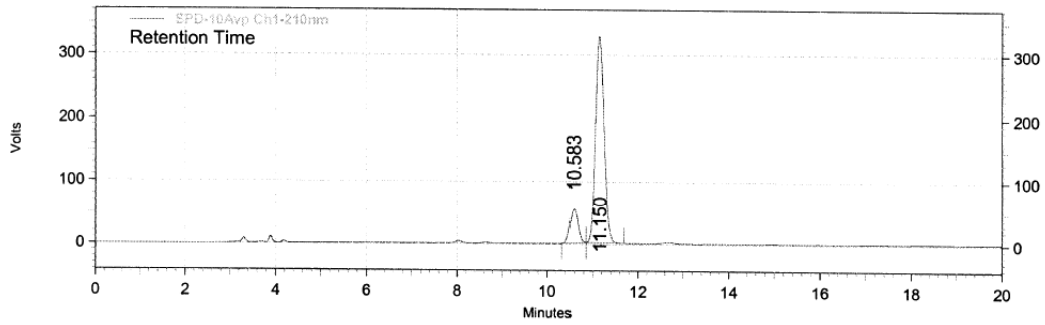
Racemic **9g** (CHIRALPAK AD-H, 95:5 Hexane:*i*-PrOH, 1 mL/min, λ = 210 nm):



SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
10.583	4549266	49.89	374750	51.95
11.150	4570094	50.11	346602	48.05

Enantiomerically enriched **9g** (74% ee):

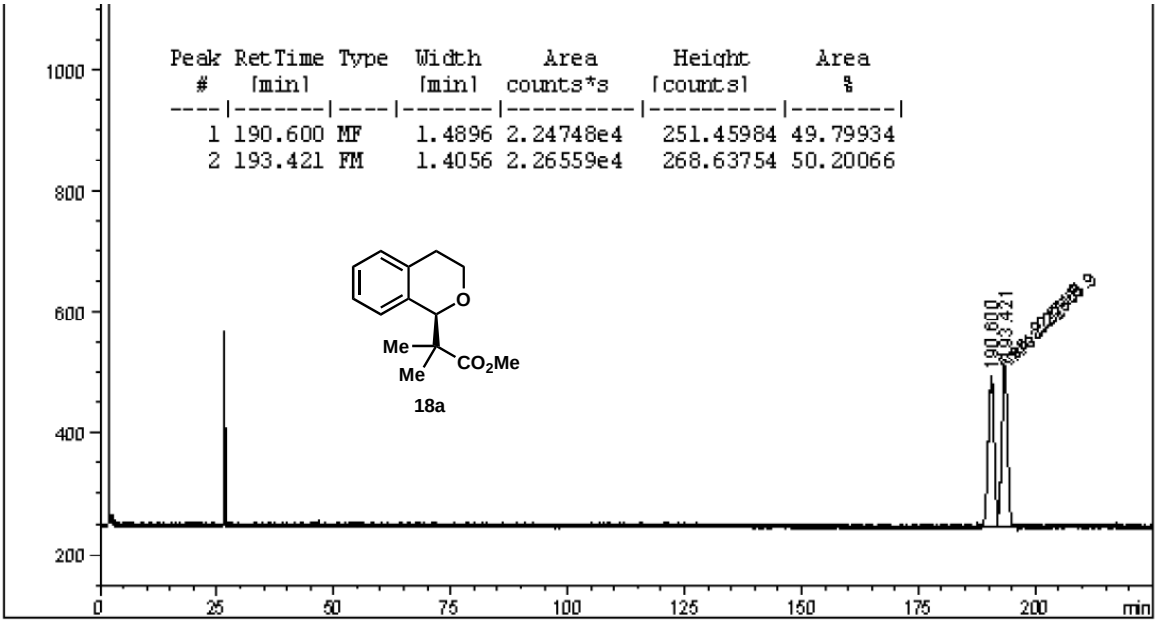


SPD-10Avp
Ch1-210nm
Results

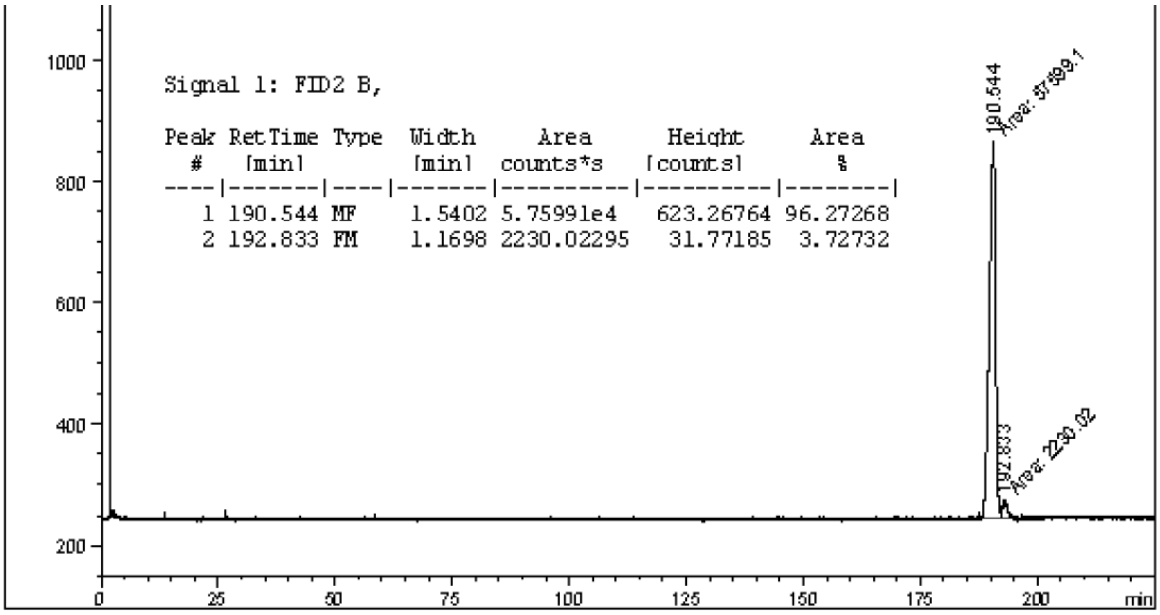
Retention Time	Area	Area %	Height	Height %
10.583	646870	12.99	55039	14.39
11.150	4333811	87.01	327332	85.61

Methyl 2-(3,4-dihydro-1*H*-isochromen-1-yl)-2-methylpropanoate (18a).

Racemic **18a** (β-cyclodex, 7 psi, 105 °C, isothermal):

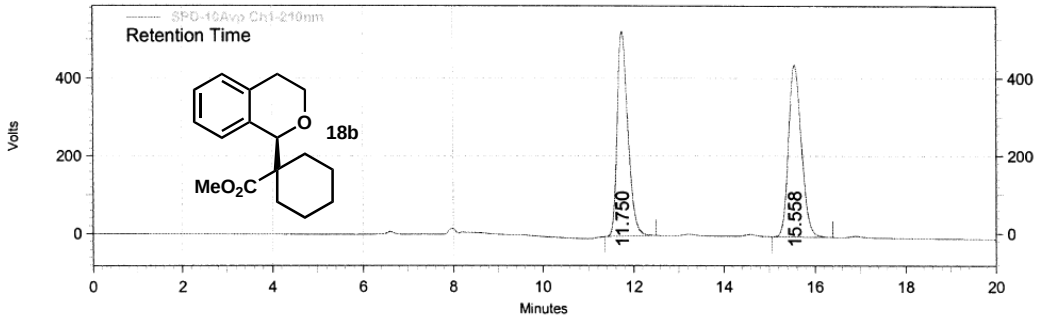


Enantiomerically enriched **18a** (92% ee):



Methyl 1-(3,4-dihydro-1*H*-isochromen-1-yl)cyclohexanecarboxylate (18b).

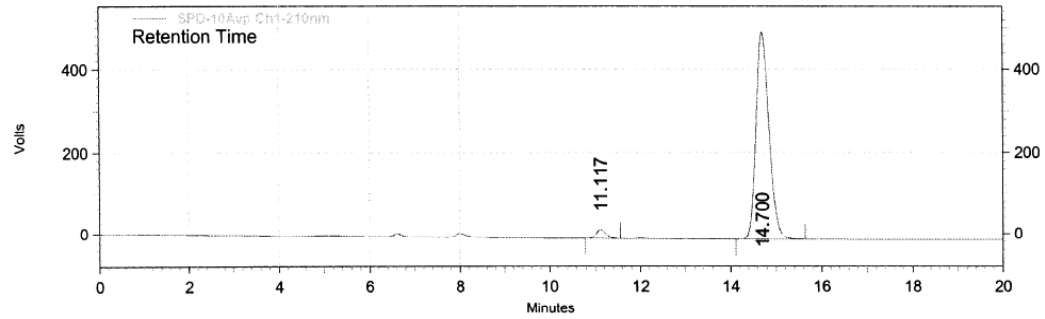
Racemic **18b** (Chiralcel OD-H, 99:1 Hexane:*i*-PrOH, 0.5 mL/min, λ = 210 nm):



SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
11.750	8750412	50.01	525662	54.29
15.558	8746123	49.99	442594	45.71

Enantiomerically enriched **18b** (94% ee):

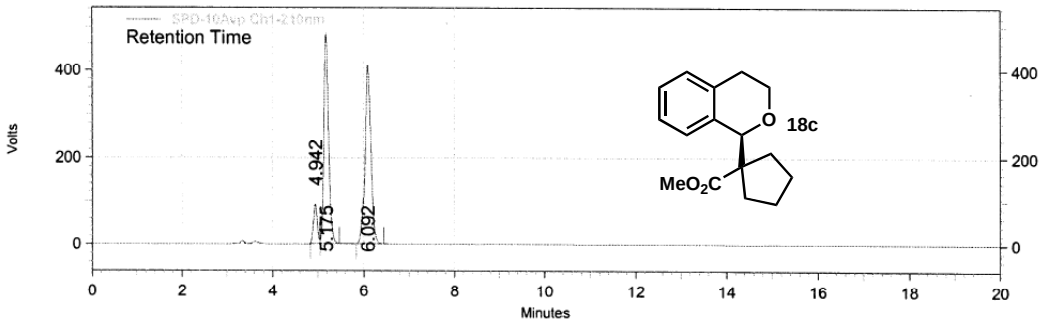


SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
11.117	327397	3.15	21365	4.07
14.700	10049761	96.85	503248	95.93

Methyl 1-((*R*)-3,4-dihydro-1*H*-isochromen-1-yl)cyclopentanecarboxylate (18c).

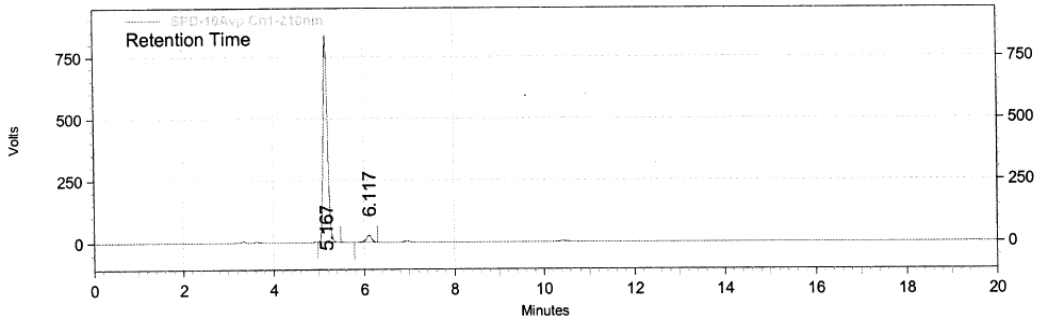
Racemic **18c** (CHIRALPAK AD-H, 98:2 Hexane:*i*-PrOH, 1.0 mL/min, λ = 210 nm):



SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
4.942	517028	6.78	89567	9.15
5.175	3413670	44.75	480169	49.03
6.092	3697342	48.47	409532	41.82

Enantiomerically enriched **18c** (92% ee):

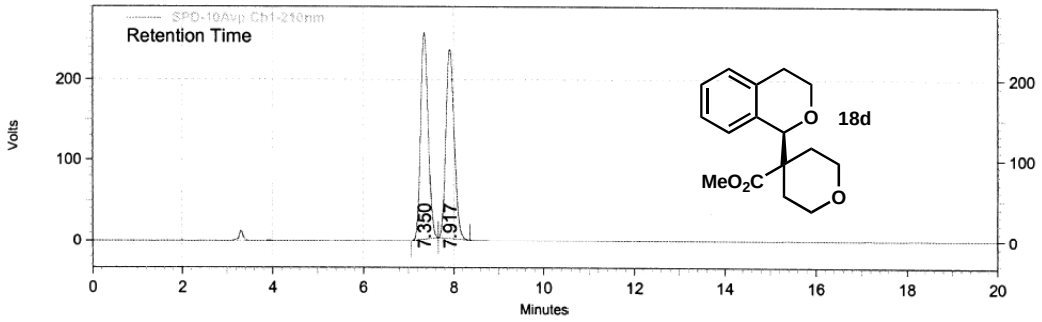


SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
5.167	5483148	95.87	835790	96.79
6.117	236299	4.13	27750	3.21

Methyl tetrahydro-4-((*R*)-3,4-dihydro-1*H*-isochromen-1-yl)-2*H*-pyran-4-carboxylate (18d).

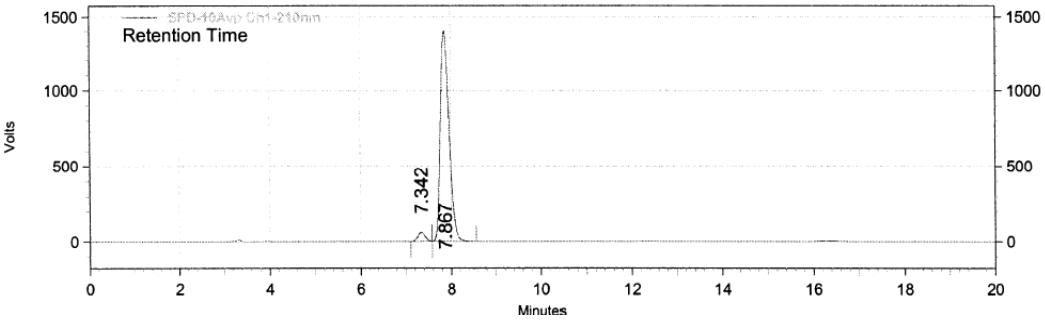
Racemic **18d** (Chiralcel OD-H, 95:5 Hexanes:*i*-PrOH, 1.0 mL/min, λ = 210 nm):



SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
7.350	2997475	49.90	256545	52.24
7.917	3009449	50.10	234499	47.76

Enantiomerically enriched **18d** (93% ee):

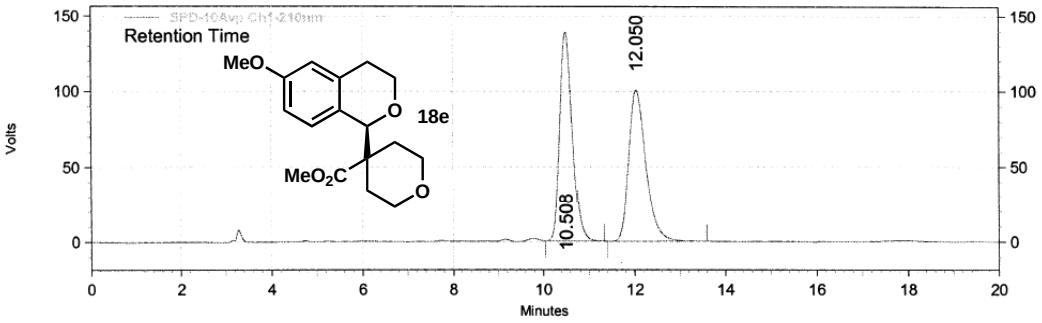


SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
7.342	669533	3.47	59513	4.09
7.867	18623659	96.53	1397312	95.91

Methyl tetrahydro-4-((*R*)-3,4-dihydro-6-methoxy-1*H*-isochromen-1-yl)-2*H*-pyran-4-carboxylate (18e).

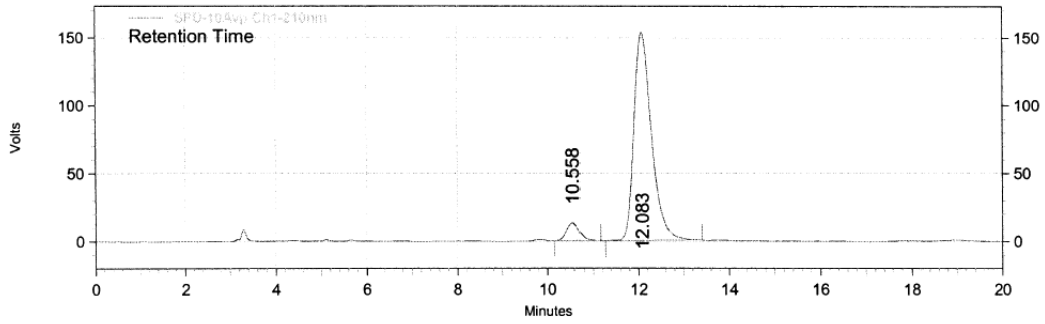
Racemic **18e** (CHIRALPAK AS-H, 95:5 Hexanes:*i*-PrOH, 1.0 mL/min, 5λ = 210 nm):



SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
10.508	2654674	49.98	138575	58.00
12.050	2656655	50.02	100333	42.00

Enantiomerically enriched **18e** (88% ee):

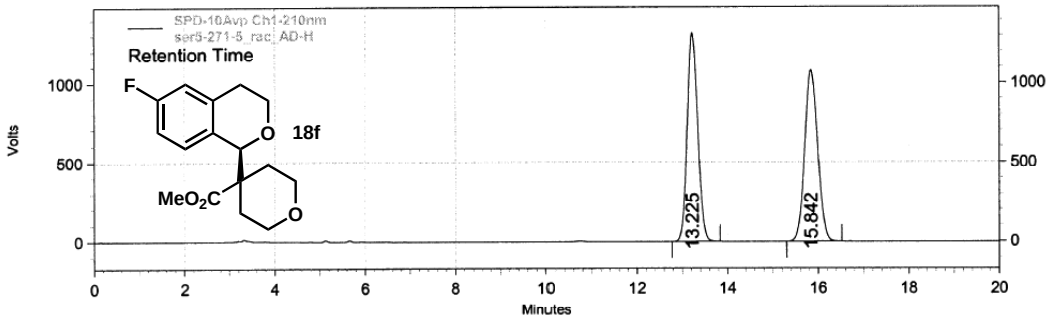


SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
10.558	252112	5.76	13097	7.87
12.083	4125516	94.24	153333	92.13

Methyl 4-((*R*)-6-fluoro-3,4-dihydro-1*H*-isochromen-1-yl)-tetrahydro-2*H*-pyran-4-carboxylate (18f).

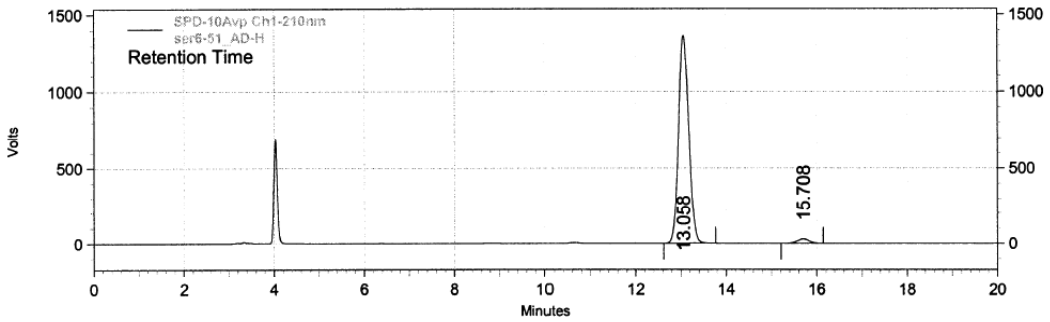
Racemic **18f** (CHIRALPAK AD-H, 95:5 Hexane:EtOH, 1.0 mL/min, λ = 210 nm):



SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
13.225	21352552	49.75	1318489	54.93
15.842	21569851	50.25	1081747	45.07

Enantiomerically enriched **18f** (95% ee):

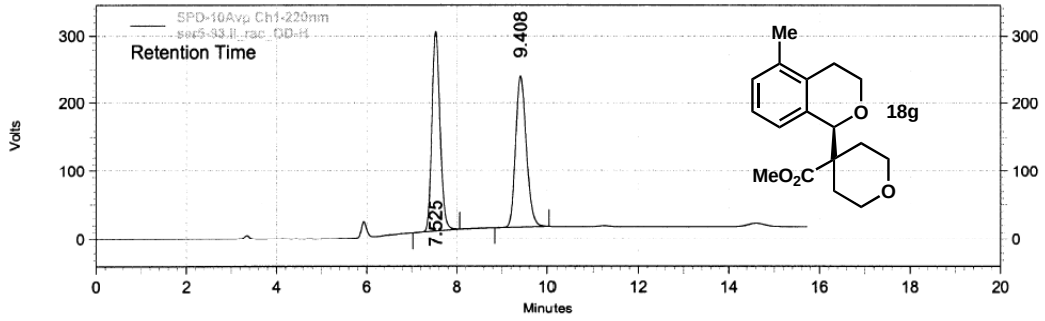


SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
13.058	21574366	97.55	1365396	97.90
15.708	541326	2.45	29226	2.10

Methyl tetrahydro-4-((*R*)-3,4-dihydro-5-methyl-1*H*-isochromen-1-yl)-2*H*-pyran-4-carboxylate (18g).

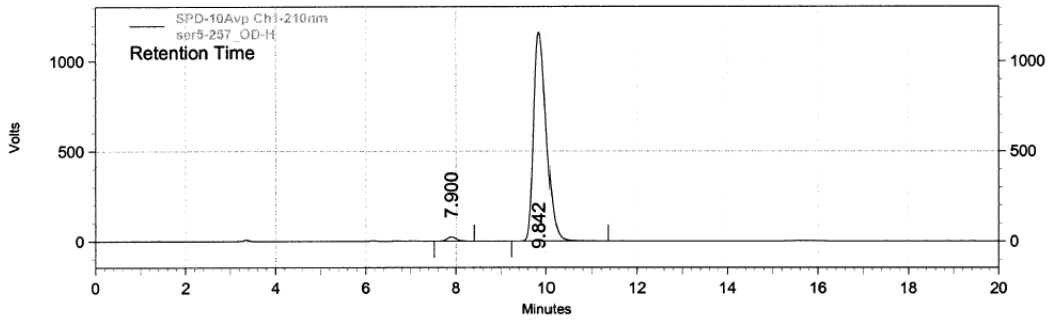
Racemic **18g** (Chiralcel OD-H, 95:5 Hexanes:*i*-PrOH, 1.0 mL/min, λ = 210 nm):



SPD-10Avp
Ch1-220nm
Results

Retention Time	Area	Area %	Height	Height %
7.525	3672578	50.02	294684	56.84
9.408	3669475	49.98	223785	43.16

Enantiomerically enriched **18g** (97% ee):

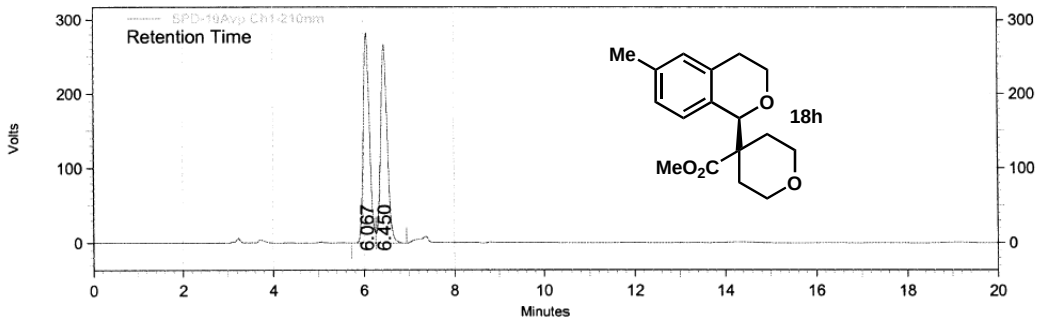


SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
7.900	347770	1.54	24581	2.07
9.842	22299138	98.46	1161221	97.93

Methyl tetrahydro-4-((*R*)-3,4-dihydro-6-methyl-1*H*-isochromen-1-yl)-2*H*-pyran-4-carboxylate (18h).

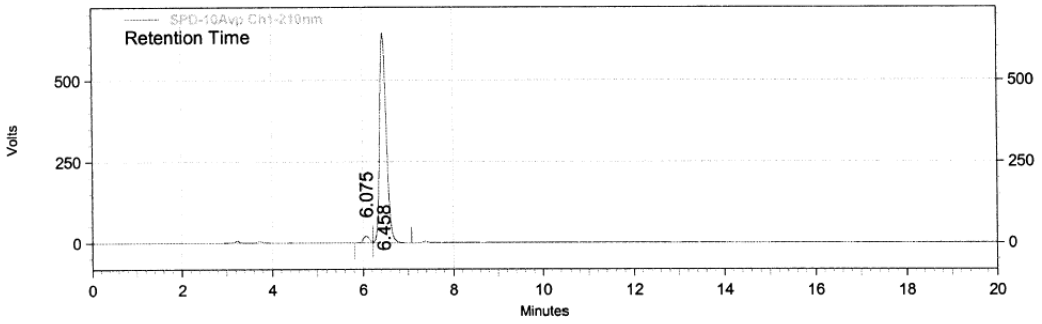
Racemic **18h** (CHIRALPAK AS-H, 98:2 Hexanes:EtOH, 1.0 mL/min, λ = 210 nm):



SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
6.067	2666243	49.40	282653	51.47
6.450	2730648	50.60	266457	48.53

Enantiomerically enriched **18h** (94% ee):

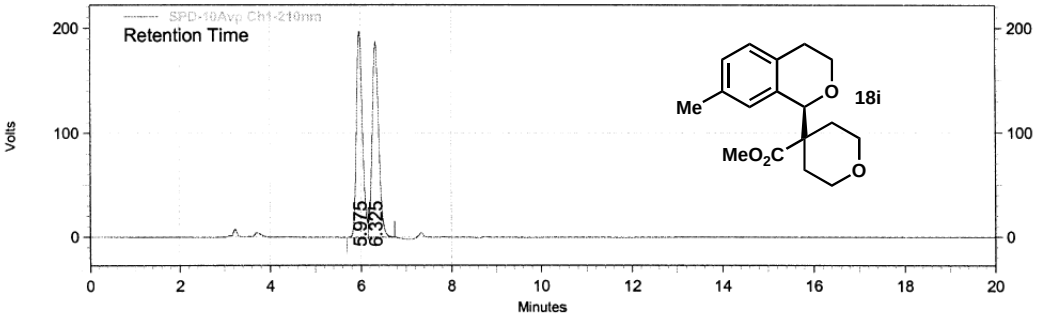


SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
6.075	196588	2.88	21034	3.17
6.458	6624153	97.12	643398	96.83

Methyl tetrahydro-4-((*R*)-3,4-dihydro-7-methyl-1*H*-isochromen-1-yl)-2*H*-pyran-4-carboxylate (18i).

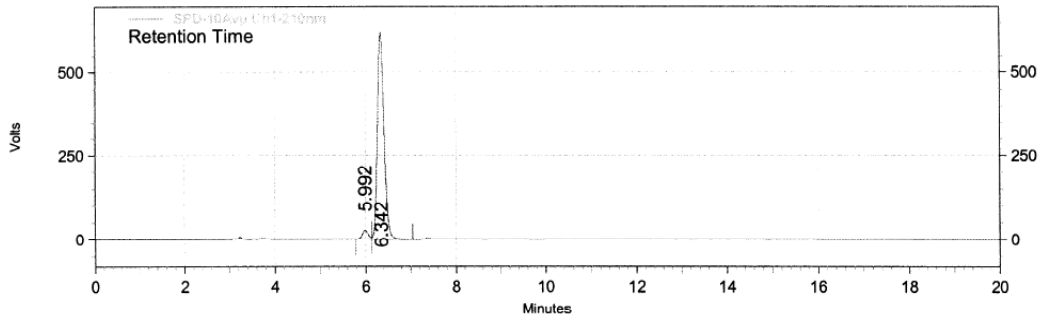
Racemic **18i** (CHIRALPAK AS-H, 98:2 Hexanes:EtOH), 1.0 mL/min, λ = 210 nm):



SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
5.975	1828714	49.30	197546	51.26
6.325	1880720	50.70	187852	48.74

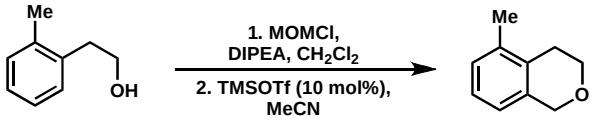
Enantiomerically enriched **18i** (92% ee):



SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
5.992	249582	3.82	27385	4.22
6.342	6291512	96.18	621040	95.78

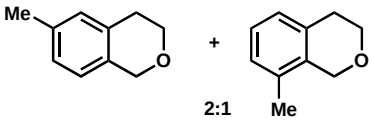
E. General procedure for the preparation of substituted isochromans: preparation of 3,4-dihydro-5-methyl-1*H*-isochromene.[5]



A solution of 2-methylphenethyl alcohol (2.7 mL, 20.0 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) was cooled to 0 ºC and DIPEA (10.5 mL, 60.0 mmol, 3.0 equiv) was added followed by MOM-Cl (2.3 mL, 30.0 mmol, 1.5 equiv). The reaction was warmed to room temperature and stirred for 14 h. The reaction was diluted with Et_2O (40 mL), washed once with aqueous 1N HCl (20 mL), once with saturated aq. $NaHCO_3$ (20 mL), once with brine (20 mL), and dried over Na_2SO_4. Filtration followed by concentration under reduced pressure provided 3.4g (94% yield) of 1-(2-(methoxymethoxy)ethyl)-2-methylbenzene. The material <95% pure by ^{1}H NMR analysis, and was used crude in the following step.

In an oven-dried 100 mL flask, 1.4 g of 1-(2-(methoxymethoxy)ethyl)-2-methylbenzene was dried by azeotrope with benzene (5 mL). The residue was dissolved in MeCN (40 mL), cooled to 0 ºC, and TMSOTf (0.14 mL, 0.78 mmol, 0.1 equiv) was added dropwise. The reaction was warmed to room temperature and stirred an additional 5 h, then quenched by addition of saturated aqueous $NaHCO_3$ (10 mL). The MeCN was removed under reduced pressure and the aqueous later was diluted with 10 mL saturated aqueous $NaHCO_3$, then partitioned with Et_2O (3 x 20 mL). The ethereal layer was dried over Na_2SO_4, filtered, and concentrated to give the crude material as a yellow oil. The crude product was purified by silica gel chromatography (gradient elution, 1:9 Et_2O:hexanes) to give 1.0g (86% yield) of 3,4-dihydro-5-methyl-1*H*-isochromene as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.12 (t, *J*=7.3 Hz, 1 H), 7.05 - 7.09 (m, *J*=7.6 Hz, 1 H), 6.87 (d, *J*=7.6 Hz, 1 H), 4.80 (s, 2 H), 4.05 (t, *J*=5.8 Hz, 2 H), 2.75 (t, *J*=5.8 Hz, 2 H), 2.27 (s, 3 H); ($CDCl_3$, 126 MHz) δ 135.5, 134.7, 130.0, 128.7, 127.1, 124.8, 67.9, 65.5, 27.9, 21.0; FTIR (NaCl, thin film) 2958, 2923, 2856, 1505, 1448, 1429, 1377, 1227, 1105, 950, 810 cm^{-1}; LRMS (ES+) m/z: 149.1 $[M+H]^+$.

3,4-dihydro-6-methyl-1*H*-isochromene and 3,4-dihydro-8-methyl-1*H*-isochromene. Followed cyclization procedure from crude 1-(2-(methoxymethoxy)ethyl)-3-methylbenzene on 3.3 mmol scale and purified using silica gel chromatography (1:9 Et_2O: Hexanes) to give 362 mg (74% yield) of an inseparable 2:1 mixture of 3,4-dihydro-6-methyl-1*H*-isochromene and regioisomeric 3,4-dihydro-8-methyl-1*H*-isochromene as a colorless oil. The oil was characterized as a mixture and carried on to the subsequent step. ^{1}H NMR ($CDCl_3$, 500 MHz; 3,4-dihydro-6-methyl-1*H*-isochromene is designated by *, 3,4-dihydro-8-methyl-1*H*-isochromene is designated by §) δ 7.11 (t, *J*=7.6 Hz, 1 H§), 6.97 - 7.03 (m, 1H*, 2 H§), 6.96 (s, 1 H*), 6.89 (d, *J*=7.8 Hz, 1 H*), 4.76 (s, 2 H*), 4.73 (s, 2 H§), 3.98 (t, *J*=5.7 Hz, 2 H*), 3.96 (t, *J*=5.6 Hz, 2 H§), 2.88 (t, *J*=5.6 Hz, 2 H§), 2.84 (t, *J*=5.7 Hz, 2 H*), 2.33 (s, 3 H*), 2.16 (s, 3 H§); ^{13}C NMR ($CDCl_3$, 126 MHz; signals for both 3,4-dihydro-6-methyl-1*H*-isochromene and 3,4-dihydro-8-methyl-1*H*-isochromene are included) δ 135.8, 133.4, 133.2, 133.1, 133.0, 131.9, 129.4, 127.5, 126.8, 126.5, 126.1, 124.3, 67.9, 66.5, 65.4, 64.9, 28.7, 28.3, 21.0, 17.8; FTIR (NaCl, thin film) 2962, 2925, 2850,1505, 1464, 1382, 1113, 1102, 950, 859, 797, 770 cm^{-1}; LRMS (ES+) m/z: 149.1 $[M+H]^+$.



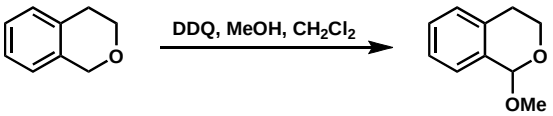
[5] DeNinno, M.P.; Perner, R.J.; Morton, H.E.; DiDomenico, S. *J. Org. Chem.* **1992**, *57*, 7115-7118.

3,4-dihydro-7-methyl-1*H*-isochromene. Followed cyclization procedure from crude 1-(2-(methoxymethoxy)ethyl)-4-methylbenzene on 5.0 mmol scale and purified using silica gel chromatography (1:9 Et_2O: Hexanes) to give 557 mg (68% yield) of 3,4-dihydro-7-methyl-1*H*-isochromene as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.04 (d, *J*=7.8 Hz, 1 H), 7.01 (d, *J*=8.0 Hz, 1 H), 6.83 (s, 1 H), 4.77 (s, 2 H), 3.99 (t, *J*=5.7 Hz, 2 H), 2.85 (t, *J*=5.7 Hz, 2 H), 2.33 (s, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 136.4, 134.7, 131.7, 127.6, 125.6, 122.0, 68.3, 65.5, 26.1, 18.7; FTIR (NaCl, thin film) 2961, 2922, 2851, 2830, 1472, 1384, 1237, 1116, 1065, 1004, 912, 855, 769 cm^{-1}, LRMS (ES+) m/z: 149.1 $[M+H]^+$

3,4-dihydro-6-fluoro-1*H*-isochromene. Followed cyclization procedure from crude 1-fluoro-3-(2-(methoxymethoxy)ethyl)benzene on 2.7 mmol scale and purified using silica gel chromatography (1:9 Et_2O: Hexanes) to give 301 mg (73% yield) of 3,4-dihydro-6-fluoro-1*H*-isochromene as a colorless oil. ^1H NMR ($CDCl_3$, 600 MHz) δ 6.84 (dd, *J*=8.2, J_{H-F}=5.7 Hz, 1 H), 6.77 (ddd, *J*=8.5, 2.3 J_{H-F}=8.5 Hz, 1 H), 6.73 (d, J_{H-F}=9.4 Hz, 1 H), 4.64 (s, 2 H), 3.86 (t, *J*=5.7 Hz, 2 H), 2.75 (t, *J*=5.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 126 Mhz) δ 161.3 (d, J_{C-F} = 244.5 Hz), 135.3 (d, J_{C-F} = 7.3 Hz), 130.4 (d, J_{C-F} = 2.8 Hz), 125.9 (d, J_{C-F} = 7.3 Hz), 115.2 (d, J_{C-F} = 21.1 Hz), 113.1 (d, J_{C-F} = 21.1 Hz), 67.6, 64.9, 28.4 (d, J_{C-F} = 2.4 Hz); FTIR (NaCl, thin film) 2927, 2873, 1617, 1591, 1515, 1490, 1451, 1247, 1149, 1110, 1073, 1033, 921, 810, 783 cm^{-1}; LRMS (ES+) m/z = 153.1 $[M+H]^+$.

3,4-dihydro-6-methoxy-1*H*-isochromene. Followed cyclization procedure from crude 1-methoxy-3-(2-(methoxymethoxy)ethyl)benzene on 30.0 mmol scale and purified by silica gel chromatography (1:9 EtOAc:Hexanes) to give 2.8g (56% yield) of 3,4-dihydro-6-methoxy-1*H*-isochromene as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 6.91 (d, *J*=8.5 Hz, 1 H), 6.76 (dd, *J*=8.4, 2.6 Hz, 1 H), 6.68 (d, *J*=2.3 Hz, 1 H), 4.74 (s, 2 H), 3.97 (t, *J*=5.7 Hz, 2 H), 3.80 (s, 3 H), 2.85 (t, *J*=5.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 126 MHz) 158.0, 134.3, 127.0, 125.3, 113.4, 112.2, 67.6, 65.1, 55.1, 28.5; FTIR (NaCl, thin film) 2956, 2934, 2835, 1611, 1504, 1453, 1382, 1313, 1274, 1243, 1157, 1102, 1038, 855, 811 cm^{-1}; LRMS (ES+) m/z = 165.1 $[M+H]^+$.

General procedure for DDQ oxidation of isochromans: preparation of 1-methoxyisochroman (6).[6,7]

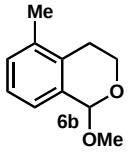


To a solution of DDQ (2.1 g, 9.3 mmol, 1.2 equiv) in CH_2Cl_2 (50 mL) was added anhydrous methanol (0.36 mL, 9.3 mmol, 1.2 equiv) followed by isochroman (1.06 g, 7.91 mmol, 1.0 equiv). The bright red heterogeneous mixture was stirred vigorously under N_2 at room temperature for 24 h, then quenched by addition of aqueous saturated $NaHCO_3$ (60 mL). The heterogeneous mixture was filtered through celite and rinsed with an additional CH_2Cl_2 (50 mL). The aqueous layer was separated and partitioned twice with 30 mL CH_2Cl_2, and the combined organic extracts were washed once with aqueous saturated $NaHCO_3$ (30 mL), once with brine (30 mL), and dried over anhydrous $MgSO_4$. The pale yellow crude oil was

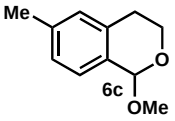
[6] Xu, Y. C.; Lebeau, E.; Gillard, J. W.; Attardo, G. *Tetrahedron Lett.* **1993**, *34*, 3841-3844.
[7] For a DDQ-mediated direct coupling of isochroman with ketones to provide racemic 1-substituted isochromans, see: Zhang, Y.; Li, Chao, Jun. *J. Am. Chem. Soc.* **2006**, *128*, 4242-4243.

purified by silica gel chromatography (10% Et_2O-Hexanes) to give 1.01 g (83% yield) of 1-methoxyisochroman (**6**) as a colorless oil. The product can also be purified by distillation through a Vigreoux column (bp = 108 °C at 15 torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 - 7.38 (m, 3 H), 7.10 - 7.22 (m, 1 H), 5.52 (s, 1 H), 4.19 (ddd, *J*=11.6, 11.6, 3.5 Hz, 1 H), 3.97 (ddd, *J*=11.4, 6.0, 1.6 Hz, 1 H), 3.61 (s, 3 H), 3.09 (ddd, *J*=17.2, 12.1, 5.9 Hz, 1 H), 2.68 (dd, *J*=14.8, 1.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ134.4, 134.3, 128.7, 128.4, 127.7, 126.6, 98.0, 58.0, 55.6, 28.2; FTIR (NaCl/thin film) 2967, 2936, 2883, 2827, 1457, 1383, 1355, 1275, 1208, 1188, 1075, 1050, 1033, 945, 954, 780, 749 cm^{-1}; LRMS (ES+) m/z = 133.1 [M–OMe]$^+$.

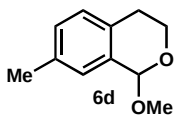
3,4-dihydro-1-methoxy-5-methyl-1*H*-isochromene (6b). Followed the general procedure on 6.7 mmol scale and purified by silica gel chromatography (1:9 to 1:3 Et_2O:Hexanes) to give 830 mg (70% yield) of 3,4-dihydro-1-methoxy-5-methyl-1*H*-isochromene as a white solid. This material contains 1-4% of the starting 3,4-dihydro-5-methyl-1*H*-isochromene. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.08 - 7.22 (m, 3 H), 5.47 (s, 1 H), 4.18 (ddd, *J*=11.6, 11.6, 3.8 Hz, 1 H), 4.00 (ddd, *J*=11.4, 6.4, 1.6 Hz, 1 H), 3.58 (s, 3 H), 2.84 (ddd, *J*=17.4, 11.9, 6.4 Hz, 1 H), 2.58 (ddd, *J*=16.7, 3.7, 1.4 Hz, 1 H), 2.26 (s, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 135.9, 133.9, 132.4, 129.4, 125.9, 125.0, 98.0, 57.4, 55.3, 25.6, 18.8; FTIR (NaCl, thin film) 2966, 2931, 2882, 2825, 1471, 1386, 1343, 1186, 1108, 1075, 1051, 955, 782, 727 cm^{-1}; LRMS (ES+) m/z: 147.3 [M–OMe]$^+$.

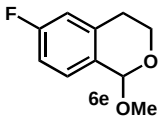


3,4-dihydro-1-methoxy-5-methyl-1*H*-isochromene (6b). Note: A 2:1 mixture of 3,4-dihydro-6-methyl-1*H*-isochromene and 3,4-dihydro-8-methyl-1*H*-isochromene was employed on 5.7 mmol scale. The selective oxidation of 3,4-dihydro-6-methyl-1*H*-isochromene was possible by modification of the general procedure to use only 0.67 equiv DDQ. The product was purified by careful silica gel chromatography (1:20 Et_2O:Hexanes, run through two columns) to give 323 mg (48% yield based on 3,4-dihydro-6-methyl-1*H*-isochromene) of 3,4-dihydro-1-methoxy-5-methyl-1*H*-isochromene as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.16 (d, *J*=7.8 Hz, 1 H), 7.06 (d, *J*=7.8 Hz, 1 H), 6.96 (s, 1 H), 5.46 (s, 1 H), 4.13 (ddd, *J*=11.6, 11.6, 3.4 Hz, 1 H), 3.92 (ddd, *J*=11.2, 6.0, 1.8 Hz, 1 H), 3.56 (s, 3 H), 3.01 (ddd, *J*=16.9, 11.9, 6.0 Hz, 1 H), 2.60 (dd, *J*=16.5, 1.6 Hz, 1 H), 2.34 (s, 3 H); ^{13}C NMR ($CDCl_3$, 126 Mhz) δ 137.8, 133.8, 131.2, 128.8, 127.2, 127.1, 97.7, 57.7, 55.2, 27.9, 21.1; FTIR (NaCl, thin film) 2927, 2880, 2825, 1619, 1382, 1355, 1187, 1132, 1091, 1075, 1048, 961, 807 cm^{-1}; LRMS (ES+) m/z 147.1 [M–OMe]$^+$.



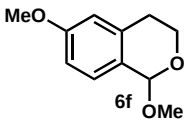
3,4-dihydro-1-methoxy-7-methyl-1*H*-isochromene (6d). Followed the general procedure on 4.6 mmol scale and purified by silica gel chromatography (1:9 Et_2O:Hexanes) to give 454 mg (60% yield) of 3,4-dihydro-1-methoxy-7-methyl-1*H*-isochromene as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.05 - 7.13 (m, 2 H), 7.03 (d, *J*=8.3 Hz, 1 H), 5.43 (s, 1 H), 4.12 (ddd, *J*=11.7, 3.4 Hz, 1 H), 3.91 (dd, *J*=11.2, 5.9 Hz, 1 H), 3.56 (s, 3 H), 3.00 (ddd, *J*=16.6, 12.2, 5.9 Hz, 1 H), 2.59 (d, *J*=16.1 Hz, 1 H), 2.33 (s, 3 H); ^{13}C NMR ($CDCl_3$,126 MHz) δ 135.9, 133.8, 130.9, 129.1, 128.3, 127.7, 97.8, 57.9, 55.3, 27.6, 21.0; FTIR (NaCl, thin film) 2928, 2879, 2826, 1505, 1352, 1158, 1095, 1074, 1049, 957, 812 cm^{-1}; LRMS (ES+) m/z: 147.3 [M–OMe]$^+$.



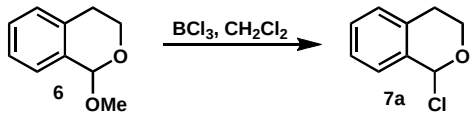


6-fluoro-3,4-dihydro-1-methoxy-1*H*-isochromene (6e). Followed the general procedure on 2.6 mmol scale and purified by silica gel chromatography (1:19 Et_2O:Hexanes) to give 303 mg (63% yield) of 6-fluoro-3,4-dihydro-1-methoxy-1*H*-isochromene as a colorless oil. This material contains 1-4% of the starting 6-fluoro-3,4-dihydro-1*H*-isochromene. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.22 (dd, *J*=8.5, $J_{H\text{-}F}$ = 5.6 Hz, 1 H), 6.93 (ddd, *J*=8.5, 2.4, $J_{H\text{-}F}$=8.5 Hz, 1 H), 6.83 (dd, *J*=2.0, $J_{H\text{-}F}$= 9.3 Hz, 1 H), 5.43 (s, 1 H), 4.10 (ddd, *J*=11.5, 11.5, 3.4 Hz, 1 H), 3.90 (dd, *J*=11.5, 6.1 Hz, 1 H), 3.54 (s, 3 H), 3.02 (ddd, *J*=17.1, 12.2, 6.3 Hz, 1 H), 2.62 (dd, *J*=16.6, 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 162.2 (d, $J_{C\text{-}F}$=247.1 Hz), 136.5, 130.1, 129.3 (d, $J_{C\text{-}F}$=8.5 Hz), 114.7 (d, $J_{C\text{-}F}$=20.5 Hz), 113.7 (d, $J_{C\text{-}F}$=21.3 Hz), 97.4, 57.2, 55.3, 28.1 (d, $J_{C\text{-}F}$=1.8 Hz); FTIR (NaCl, thin film) 2936, 2983, 1621, 1593, 1500, 1384, 1272, 1240, 1107, 1075, 1050, 1000, 964, 837 cm^{-1}, LRMS (ES+) m/z 151.0 [M–OMe]$^+$.

6-methoxy-3,4-dihydro-1-methoxy-1*H*-isochromene (6e). Followed the general procedure on 2.6 mmol scale and purified by silica gel chromatography (5:1 EtOAc:Hexanes) to give 307 mg (55% yield) of 6-methoxy-3,4-dihydro-1-methoxy-1*H*-isochromene as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.17 (d, *J*=8.5 Hz, 1 H), 6.79 (dd, *J*=8.5, 2.5 Hz, 1 H), 6.65 (d, *J*=2.3 Hz, 1 H), 5.43 (s, 1 H), 4.11 (ddd, *J*=11.6, 11.6, 3.4 Hz, 1 H), 3.89 (ddd, *J*=11.3, 6.1, 1.6 Hz, 1 H), 3.79 (s, 3 H), 3.53 (s, 3 H), 3.01 (ddd, *J*=17.2, 12.1, 6.2 Hz, 1 H), 2.60 (dd, *J*=16.6, 1.7 Hz, 1 H); ^{13}C NMR (126 MHz) δ 159.2, 135.5, 128.6, 126.7, 112.8, 112.7, 97.7, 57.5, 55.2, 55.1, 28.3; FTIR (NaCl, thin film) 2937, 2881, 2828, 1612, 1504, 1466, 1382, 1321, 1277, 1248, 1127, 1074, 1046, 959, 835 cm^{-1}; LRMS (ES+) m/z = 163.1 [M–OMe]$^+$.

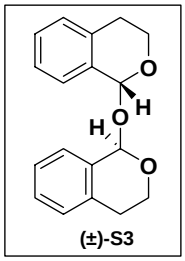


Preparation of 1-chloroisochroman (7a).



A flame-dried 25 mL flask was charged with 1-methoxyisochroman (**6**, 1.52g, 9.29 mmol, 1.0 equiv) and flushed with N_2, then CH_2Cl_2 was added (7.4 mL). The solution was cooled to 0 °C and BCl_3 (1.0 M solution in hexanes, 3.7 mL, 3.7 mmol, 0.4 equiv) was added dropwise over 5 min. A yellow precipitate was observed, and the mixture was stirred 5 min at 0 °C then warmed to room temperature. After 5 min at room temperature, the reaction was a homogenous pale yellow solution. Stirring was continued for 1.5 h, after which time the reaction flask was quickly fitted with an oven-dried vac-transfer tube and receiving flask under N_2, the receiving flask was cooled to –78 °C, and the solvent was removed in vacuo (1 torr). Once the solvent was removed, the system was back-filled with N_2 and the vac-transfer tube was quickly exchanged for an oven-dried short path distillation head. The crude yellow oil was distilled in vacuo to give **7a** as a viscous, colorless oil (1.15 g, 74% yield, bp=78 °C at 0.5 torr). ^{1}H NMR (C_6D_6, 500 MHz) δ 7.00 (dd, *J*=7.1, 1.8 Hz, 1 H), 6.93 (s, 1 H), 6.85 - 6.92 (m, 2 H), 6.66 (dd, *J*=6.9 Hz, 1 H), 4.14 (ddd, *J*=11.7, 11.7, 3.2 Hz, 1 H), 3.62 (dd, *J*=11.3, 6.3 Hz, 1 H), 2.57 (ddd, *J*=16.9, 13.0, 6.4 Hz, 1 H), 1.90 - 2.02 (m, 1 H); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.22 - 7.32 (m, 3 H), 7.16 (s, 1 H), 7.14 (d, *J*=6.4 Hz, 1 H), 4.38 (br. s, 1 H), 4.17 (br. s, 1 H), 3.14 (br. s, 1 H), 2.76 (br. s, 1 H); ^{13}C NMR (C_6D_6, 126 MHz) δ 135.0, 132.1, 128.9, 128.5, 127.0, 126.7, 93.7, 60.3, 26.9; ^{13}C NMR ($CDCl_3$, 126 MHz) δ 135.6, 132.4, 128.7, 128.5, 127.4, 126.7, 93.8, 60.2, 26.9; compound readily undergoes hydrolysis under typical FTIR and mass spectrometry conditions.

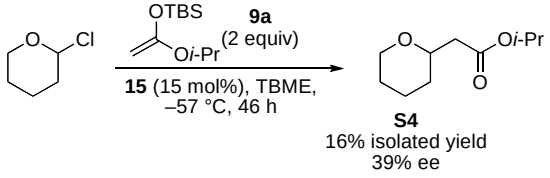
The purified material was stored in a sealed flask under N_2 in a –80 °C freezer. 1-Chloroisochroman (**7a**) undergoes rapid hydrolysis when exposed to moist air to give the dimeric compound **S3**.[8] However, **7a** was stored as described above for 4 months or longer without detectable hydrolysis or decomposition.



F. Thiourea-catalyzed additions to alkyl chloroether substrates.

Preliminary results have been obtained for the substitution of silyl ketene acetal **9a** to 2-chloro-tetrahydro-2*H*-pyran catalyzed by thiourea **15**. Whereas the yields and selectivities observed at –57 °C are modest, reactions conducted under the same conditions in the absence of **15** fail to produce any detectable addition product **S4**. Moreover, experiments conducted in the absence of **15** at room temperature still provide <5% **S4** after 24h. These data suggest that alkyl chloroethers represent a challenging yet viable class of substrates for thiourea-catalyzed substitution reactions. The development of more selective catalysts for this type of substrate class is the focus of continued research.

Addition of silyl ketene acetal 9a to 2-chloro-tetrahydro-2*H*-pyran[9] catalyzed by thiourea 15.



An oven-dried 10 mL flask was charged with thiourea catalyst (25.8 mg, 0.047 mmol, 0.16 equiv), flushed with N_2, and TBME (1.0 mL) was added. The flask was cooled to –78 °C and **9b** was added (0.150 mL, 0.60 mmol, 2.0 equiv), followed by 2-chloro-tetrahydro-2*H*-pyran (0.40 mL of a 0.73 M stock solution in TBME, 0.29 mmol, 1.0 equiv). The reaction was maintained at –57 °C for 46 h, then quenched at that temperature by addition of NaOMe (0.2 mL of 0.5 M solution in MeOH). The reaction was diluted with 1 mL of 50% Et_2O-Hexanes soution, filtered through a pipette containing ¾ inch of silica gel (to hydrolyze remaining silyl ketene acetal), and rinsed with 5 mL of the 50% Et_2O-Hexanes solution. The solvent was removed by rotary evaporation under reduced pressure. Analysis of the crude reaction mixture by ^{1}H NMR versus an internal standard determined that isopropyl 2-(tetrahydro-2*H*-pyran-2-yl)acetate (**S4**) was formed in 39% yield. Purification by silica gel chromatography (1:9 EtOAc:Hexanes) provided **S4** (9.0 mg, 16% yield) as a colorless oil. The enantiomeric excess was determined to be 39% by chiral GC analysis (γ-TA, 60° C isothermal, 7 psi): t_R(major)=98.0 min,

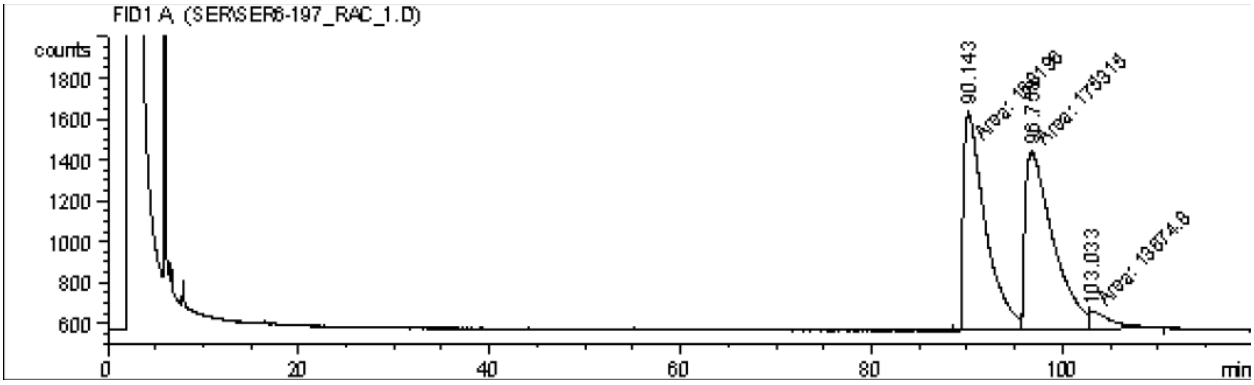
[8] Dimer **S3** is a known compound. See reference 6.
[9] Prepared by the method of Viola and coworkers. Viola, A.; Collins, J.J.; Filipp, N.; Locke, J.S. *J. Org. Chem.* **1993**, *58*, 5067–5075.

t_R(minor)=91.8 min. $[\alpha]_D^{27}$ = 5° (c = 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.03 (sept, *J*=6.4 Hz, 1 H), 3.95 (ddd, *J*=11.4, 3.9, 2.1 Hz, 1 H), 3.73 (dddd, *J*=10.3, 7.8, 5.5, 2.3 Hz, 1 H), 3.45 (ddd, *J*=11.4, 2.7 Hz, 1 H), 2.48 (dd, *J*=14.9, 7.8 Hz, 1 H), 2.34 (dd, *J*=14.9, 5.5 Hz, 1 H), 1.77 - 1.88 (m, 1 H), 1.61 - 1.67 (m, 1 H), 1.46 - 1.60 (m, 3 H), 1.26 - 1.36 (m, 1 H), 1.23 (dd, *J*=6.3, 3.5 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 170.9, 74.4, 68.5, 67.7, 42.0, 31.5, 25.7, 25.6, 23.3, 21.8; FTIR (NaCl, thin film) 2979, 2937, 2857, 1736, 1375, 1294, 1252, 1169, 1111, 1090, 1046 cm^{-1}; LRMS (ES+) m/z = 209.1 $[M+Na]^+$.

To facilitate determination of conversion by ^{1}H NMR analysis of the crude reaction mixtures, the 2-chloro-tetrahydro-2*H*-pyran stock solution contained 0.12 equiv of isochroman as an internal standard.

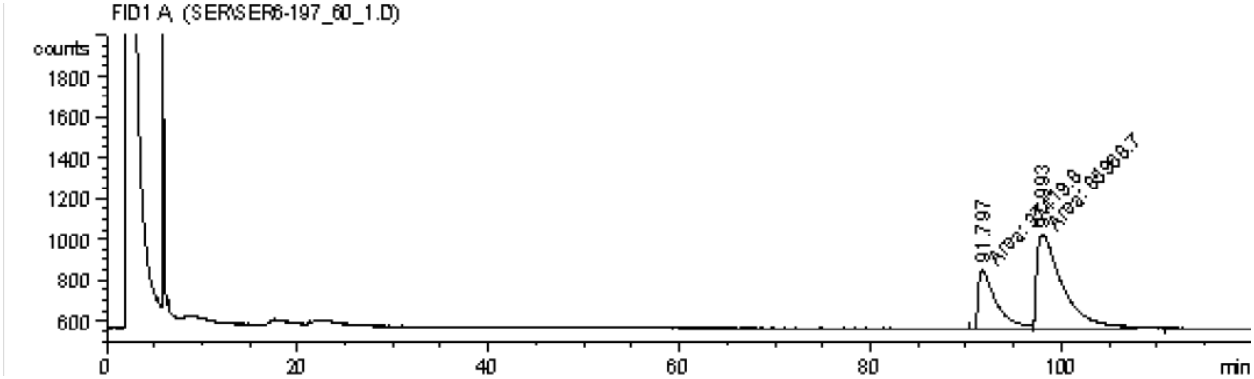
Isopropyl 2-(tetrahydro-2*H*-pyran-2-yl)acetate (S4).

Racemic **S4** (Gamma-TA, 60° C isothermal, 7 psi):



Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	90.143	MF	2.6221	1.68196e5	1069.08411	47.08929
2	96.758	MF	3.3292	1.75315e5	877.65173	49.08221
3	103.033	FM	2.6035	1.36748e4	87.54256	3.82849

Enantiomerically enriched **S4** (39% ee):



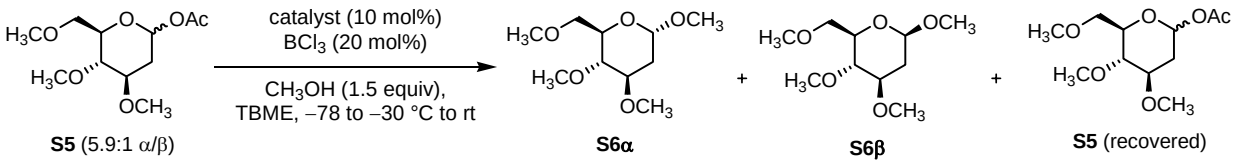
Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	91.797	MF	2.1399	3.74198e4	291.44708	30.32682
2	97.993	FM	3.0836	8.59687e4	464.65515	69.67318

Preliminary efforts toward thiourea catalyst-controlled diastereoselective O-glycosidations

Methods for stereoselective 2-deoxyglycosyl bond-formation are particularly challenging due to the lack of a stereodirecting C–2 substituent that can participate in anchimeric assistance during the bond-forming step.[10] 2-Deoxyglycosides are also found in several important antibiotic families, including the erythromycins, and the anthracycline and enediyne antibiotics. Considering these two possibilities, we chose to examine 2-deoxy glycosyl donors as substrates for the thiourea-catalyzed addition reactions.

Promising preliminary results were found for O-glycosidation reactions. In particular, significant rate accelerations for the addition of alcohols to glycosyl acetates were observed in the presence of thiourea catalyst **14** and 20 mol% BCl_3 (SI Table 1).[11] In the absence of catalyst, addition of methanol to **S5** proceeds in only 19% conversion over 48 h at –30 °C and results in a 1:1.1 α/β ratio of product **S6**. By contrast, using (*R*,*S*)-**14**, 1-methoxy **S6** was formed in 94% conversion and in 1:1.7 ratio in favor of the β anomer. Use of the opposite enantiomer of catalyst (*S*,*R*)-**14** led to a small preference for the formation of the α anomer in a 1.4:1 ratio. Analysis of the stereochemical outcome of the reaction is complicated by the fact that substrate **S5** exists as a mixture of α and β anomers. Recovered starting material from the reactions with (*R*,*S*) and (*S*,*R*)-**14** showed that the two diastereomers react at different rates with the enantiomeric catalysts. Thus, it is clear that the catalyst imparts some degree of stereocontrol in the reaction and experiments are ongoing to improve upon these preliminary results.

SI Table 1. Doubly diasteroselective O-glycosidation of **S5** with chiral thiourea **14**.

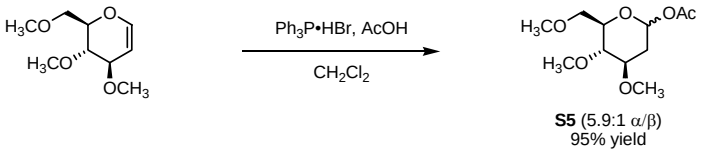


entry	catalyst	conv. (%)[a]	α/β (**S6**)[a]	α/β (**S5**)[a]
1	none	19	1:1.1	>15:1
2	(*R*,*S*)-**14**	94	1:1.7	>15:1
3	(*S*,*R*)-**14**	56	1.4:1	8.9:1

[a]Determined by ^{1}H NMR analysis.

General procedure for the preparation of 3,4,5-tri-O-methyl-2-deoxy glycosyl acetate (S5):

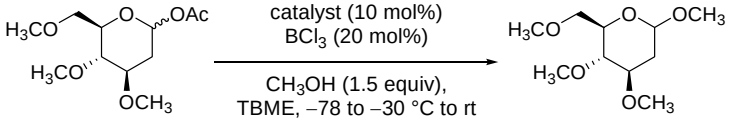
[10] For a recent review, see: Marzabadi, C. H.; Franck, R. W. *Tetrahedron* **2000**, *56*, 8385–8417.
[11] BCl_3-catalyzed O-glycosidations have been reported: Toshima, K.; Nagai, H.; Ushiki, Y.; Matsumura, S. *Synlett* **1998**, 1007–1009.



S5 (5.9:1 α/β)
95% yield

An oven-dried 100 mL round-bottom flask was charged with 3,4,6-tri-*O*-methyl-D-glucal[12] (2.12 g, 11 mmol, 1 equiv), 55 mL dichloromethane, and a stir bar. Glacial acetic acid (1.0 mL, 16.5 mmol, 1.5 equiv) and PPh_3·HBr (189 mg, 0.55 mmol, 5 mol%) were added. The reaction was stirred for 21.5 hours at room temperature and then the reaction was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with 15% to 20% to 25% ethyl acetate in hexanes to give acetate **S5** as a clear oil (2.60 g, 95% yield). ^{1}H NMR ($CDCl_3$, 500 MHz; compound exists as a 5.9:1 mixture of α and β anomers, the major anomer is denoted by *) δ 6.22 (1 H*, dd, *J*=3.4, 1.5 Hz), 5.67 (1 H, dd, *J*=10.0, 2.2 Hz), 3.70 (1 H*, ddd, *J*=9.8, 3.4, 2.0 Hz), 3.57 (3 H*, s), 3.55 (3 H, s), 3.53 - 3.65 (3 H* + 2 H, m), 3.46 (3 H*, s), 3.45 (3 H, s), 3.41 (3 H*, s), 3.40 (3 H, s), 3.35 - 3.43 (2 H, m), 3.26 (1 H*, dd, *J*=9.8 Hz), 3.21 (1 H, dd, *J*=9.3 Hz), 2.33 (1 H, ddd, *J*=12.3, 5.0, 2.2 Hz), 2.24 (1 H*, ddd, *J*=13.6, 5.2, 1.7 Hz), 2.09 (3 H, s), 2.08 (3 H*, s), 1.69 (1 H*, ddd, *J*=13.7, 11.2, 3.4 Hz), 1.55 - 1.63 (1 H, m); ^{13}C NMR ($CDCl_3$, 125 MHz; compound exists as a 5.9:1 mixture of α and β anomers, signals corresponding to the major anomer are provided) δ 169.5, 92.3, 79.5, 78.4, 73.4, 71.2, 60.8, 59.4, 57.5, 33.9, 21.3; FTIR (thin film, cm^{-1}) 3616 (br), 3523 (br), 2980 (s), 2934 (s), 2831 (s), 1746 (s), 1447 (s), 1377 (s), 1237 (s), 1189 (s), 1129 (s), 1073 (s), 1014 (s), 992 (s), 970 (s), 926 (s), 887 (m); HRMS (ES+) $[M+K]^+$ calculated for $C_{11}H_{20}KO_6$: 287.0892, Found: 287.0898.

General procedure for thiourea-catalyzed addition of methanol to of 3,4,6-tri-O-methyl-2-deoxy glycosyl acetate (SI Table 1, entries 1−3).



S5 (5.9:1 α/β) **S6**

An oven-dried 1-dram vial containing a stir bar and fitted with a screw cap lid containing a Teflon septum was cooled under a nitrogen atmosphere. The vial was charged with thiourea catalyst (0.01 mmol, 10 mol%) and the vial was evacuated and backfilled with nitrogen. To the vial was added glycosyl acetate **S5** (0.80 mL of a 0.125 M stock solution in TBME, 0.1 mmol, 1 equiv) and the solution was cooled to −78 °C (dry ice-acetone bath). Methanol (6mL, 0.15 mmol, 1.5 equiv) was added via syringe, followed by BCl_3 (20 mL, 1 M solution in hexanes, 0.02 mmol, 20 mol%). The vial was immediately transferred to a −30 °C immersion cooler and was maintained at that temperature for 48 hours. The reaction was warmed to room temperature over 10 minutes and filtered through a pipette containing 2 inches of silica gel and rinsed with 10 mL of a 50% Et_2O-Hexanes solution. The solvent was removed by rotary evaporation under reduced pressure to give the crude residue **S6**, which was analyzed by ^{1}H NMR to determine the reaction conversion and diastereoselectivity. The

[12] Prepared from D-Glucal based on the procedure reported in: Dunkerton, L. V.; Adair, N. K.; Euske, J. M.; Brady, K. T.; Robinson, P. D. *J. Org. Chem*. **1988**, *53*, 845−850. D-Glucal was prepared according to the literature procedure: Di Bussolo, V.; Caselli, M.; Pineschi, M.; Crotti, P. *Org. Lett*. **2003**, *5*, 2173−2176.

diastereomeric ratio of product was determined by ^{1}H NMR integration ($\delta_{H1,\alpha}$ = 4.82 ppm, $\delta_{H1,\beta}$ = 4.35 ppm). The diastereomeric ratio of recovered starting material was determined by ^{1}H NMR integration ($\delta_{H1,\alpha}$ = 6.22 ppm, $\delta_{H1,\beta}$ = 5.67 ppm). ^{1}H NMR ($CDCl_3$, 500 MHz; compound exists as a mixture of α and β anomers, the major anomer is denoted by *) δ 4.82 (1 H*, d, *J*=2.4 Hz), 4.35 (1 H, dd, *J*=9.8, 2.0 Hz), 3.55 - 3.69 (4 H* + 2 H, m), 3.54 (3 H*, s), 3.54 (3 H, s), 3.49 (3 H, s), 3.44 (3 H*, s), 3.43 (3 H, s), 3.43 (3 H*, s), 3.42 (3 H, s), 3.33 (3 H*, s), 3.24 - 3.34 (2 H, m), 3.16 (1 H*, dd, *J*=9.3 Hz), 3.11 (1 H, dd, *J*=9.3 Hz), 2.30 (1 H, ddd, *J*=12.7, 5.4, 2.0 Hz), 2.22 (1 H*, ddd, *J*=13.1, 5.0, 1.5 Hz), 1.56 (1 H*, ddd, *J*=13.1, 11.6, 3.7 Hz), 1.48 (1 H, ddd, *J*=12.2, 9.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz; compound exists as a mixture of α and β anomers, signals corresponding to the major anomer are denoted by *) δ 101.0, 98.7*, 81.1, 80.1*, 79.8, 78.9*, 75.2, 71.9, 71.6*, 70.6*, 60.7, 60.6*, 59.5, 59.4*, 57.4*, 57.1, 56.7, 54.8*, 36.1, 35.0*; FTIR (thin film, cm^{-1}) 2977 (m), 2934 (s), 2896 (s), 2832 (s), 1467 (m), 1447 (m), 1385 (m), 1214 (s), 1188 (s), 1128 (s), 1083 (s), 996 (m), 972 (s), 905 (m); HRMS (ES+) $[M+Na]^+$ calculated for $C_{10}H_{20}NaO_5$: 243.1203, Found: 243.1223.